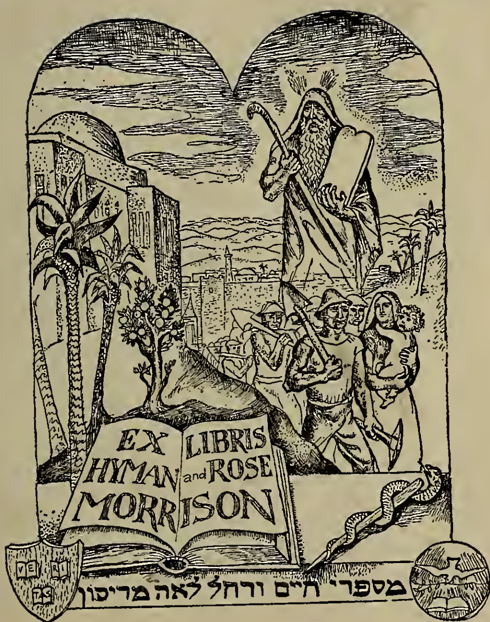
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LECTURES

ON

DISEASES OF THE DIGESTIVE ORGANS.

BY

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Translated from the latest German Edition

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PREFACE TO THE ENGLISH EDITION.

THE publication of a work by the New Sydenham Society indicates such a kindly appreciation of its merits by eminent members of our profession, and is such an honourable recognition of the author, that it is his first and plainest duty to give expression to his sincere thanks and gratification at the distinction shown to him. Whilst I do this with all my heart, I hope that the reception of these "Lectures on Diseases of the Digestive Organs" may be as favourable in England as elsewhere. I was not led to concern myself with the disorders of digestion by clinical study. My way led through physiology, and when, in 1879, I published the first edition of the first part of these lectures, the diseases of the digestive organs were just beginning to be studied by means of new methods of investigation. I happened to take a modest share in this work, and half against my will I gathered a large practical experience. The "Diseases of the Stomach" is a review of these methods, and a statement of their pathognostic, diagnostic, and therapeutic results. The investigators in this field are still enthusiastic in their work, and in the two years which have passed since the publication of the second German edition of this part, many questions have been cleared up, which then were in the midst of discussion, and much that is new has been added. I have endeavoured to remedy this by making short additions to the text, and I owe special thanks to Dr. Saundby for the great care he has devoted to his excellent translation. I can say

that on the whole the progress of investigation has confirmed my formerly expressed ideas, and that the later work has not required any important changes.

Perhaps I am wrong, but it appears to me that the new methods of investigating the activity of the stomach functions have not so far become so popular in England as their diagnostic and therapeutic worth deserves. It would be a great satisfaction to the author if his book might help to point out how easy these investigations are, and how important, under certain circumstances, they may become.

C. A. EWALD.

BERLIN, *October*, 1891.

TRANSLATOR'S PREFACE.

I HAVE much pleasure in presenting to my English *confrères* this translation of Professor Ewald's well-known lectures. In 1880 I published a translation of the first edition of his "Lectures on Digestion," which constitute Vol. I., but the present translation is from the third German Edition of 1890, which was, to a great extent, re-written and much enlarged. Vol. II. has not been previously translated, and is not familiar to English readers. Without pretending to endorse all it contains, I am satisfied that the views expressed are, in the main, sound, consistent, and thoroughly practical.

ROBERT SAUNDBY.

BIRMINGHAM,
November, 1891.

LECTURES ON DIGESTION.

LECTURE I.

Gentlemen,—More than anywhere else, in diseases of the digestive organs it is possible to avert permanent injury, and to carry out rational and successful therapeutics, by a clear and just appreciation of physiological processes. Digestion is comparable to a complicated clock-work, the derangements of which are readily shown by the movements of the hands, but the causes of which are difficult to discover, from the complexity and concealed position of the movement. Therefore the pathology of digestion requires a well-grounded knowledge of the complex processes which effect the transformation of our food into chyle.

This is so plain as scarcely to need to be referred to, as it is unintelligible how any one could come to any conclusion as to the causes of defective action in a clock from inspecting the hands, instead of looking at the works. Such superficial inquiry could only lead to blunders.

But the physiology of digestion has during recent years developed as scarcely any other branch of the subject has done, both in breadth and depth, and a notable list of new observations and brilliant discoveries give it quite another aspect to that which it possessed fifteen or twenty years ago. A great mass of histological and physiological details, which teach us the intimate nature of special processes, and the discovery of chemical facts which have led to the attainment of new general points of view, have much elucidated its aspect, filled up many gaps, and turned the current of investigation into quite new channels.

The classical works of Joh. Müller, Tiedemann, Gmelin, Frerichs, Bidder and Schmidt, stand out as landmarks and indications of the contemporary position of science; but the task belongs to me to follow its development from their time to our

own. This is a protracted task, owing to the condition of our literature, as the information is scattered through a hundred monographs, periodicals, and reviews. In order that I may give the desired attention to our recent knowledge, and bearing in mind our special object, the relation of derangements of the digestion to our knowledge of the normal processes, I think it best, in the following remarks, to treat chiefly of new facts and theories, and to recapitulate briefly what is generally known, as a sort of foundation on which to place our corner-stone. I am anxious, therefore, in the recital of facts, to speak only of the *modus operandi* in its grosser features, and to give chemical formulæ and methods only so far as is necessary to make the subject intelligible. On the other hand, I will willingly linger over the clinical aspects whenever a suitable occasion offers for a glance at practical points, and especially from a therapeutic point of view.

Proceeding in this fashion, we shall first have to learn not only a general outline of the knowledge we possess, but also the numerous gaps and defects in it, for in order to obtain a clear insight into a subject, the knowledge of our deficiencies is the first step towards progress.

Let us then see what is understood by the term "Digestion."

By *digestion* is generally meant that which belongs to the animal kingdom—that is to say, the processes by which nutriment is prepared for absorption into the circulation, and for further use in the animal economy. Plants do not digest, and have, in an ordinary sense, no digestive organs, so that it might appear that this made a fundamental distinction between the animal and vegetable kingdoms, if we restricted ourselves to the morphological stand-point. But if we regard the digestive process more broadly, as has been done by the genius of Claude Bernard, we see that no such distinction holds good, but that both throughout possess a common type as their base.

If we follow out the processes of digestion from the surface of the alimentary canal of an animal, by which the crude nutriment is changed into material for cell-nutrition, and the changes it undergoes in the various organs, or in the circulation, or finally in the cells themselves, we perceive that it may be divided into two kinds, *Superficial* and *Interstitial*, and that these are present in plants as well as in animals. Certainly in very different degrees, for it must not be forgotten that the process of digestion in

plants is concerned in assimilating not complex organic molecules, but easily diffusible gases and simple compounds, chiefly carbonic acid and water, with salts in solution.

Superficial digestion occurs on the surface of organs or organisms, and is that which we call digestion in its proper sense in animals. As the intestinal tract is formed by a canal open above and below, into which the various glands of the body debouch, we may regard the treatment of nutriment in the stomach and intestine of animals as a superficial process taking place on an inner surface of the body. In this respect there is a great analogy with plants, *i.e.*, a superficial digestion occurs, though of not nearly so obvious a kind as in animals. For plants which have no chlorophyll it is apparently the rule and first condition of life. Yeast cells, for example, require for their nutriment a solution of invert sugar, a mixture of dextrose and lævulose, and cannot grow in a pure solution of cane sugar. But each yeast cell possesses the power of converting cane sugar into invert sugar, which is a kind of superficial digestion, a process effected by means of a ferment quite analogous to that which occurs in animals. But higher plants also present the same relations.

By the beautiful researches of Darwin we are familiar with the processes in the so-called insectivorous plants, the *Drosera rotundifolia*, the *Dionioea muscipula*, &c., and we know that their leaves possess the power of secreting a peculiar acid juice which flows over small insects entangled and held fast in the leaf-hairs, or pieces of albumen laid upon them, and prepares them for absorption by the leaf-vessels. These peculiar relations of the leaf surface offer a complete analogy to the stomach digestion of animals, especially of the lower animals, where, as in the amœba, any part of the surface of the body may by invagination form a sort of stomach for the reception of nutriment.

There can be no doubt, therefore, that superficial digestion in its essential form does occur in plants, so that we cannot regard this kind of digestion as exclusively the property of animals. But all this is true in a much higher and more complete degree of *interstitial digestion*, indeed the relation between the vegetable and animal kingdom is almost reversed. Plants and animals store up in their cells a wealth of nutriment, so that they can exist for a certain time, some more, others less, without taking in nutriment. This material, deposited in an insoluble form,

undergoes changes by the action of ferments into soluble products, which pass into the circulation, forming a sort of digestion not to be distinguished from the kind previously described, except that it is not performed in special organs, but may take place in every cell in the organism, and commit its products direct to the interstitial circulation. This it is which was called by Claude Bernard *interstitial digestion.* It deals with carbo-hydrates, albuminates, and fats in special ways, of which we only know exactly the fate of the carbo-hydrates. They are developed most widely in the vegetable kingdom, where from their special prominence they must play a most important part; but they are to be met with in the same fashion in animals.

The change in the sprouting nodes of plants of insoluble starch in soluble sugar, and the transformation of glycogen in the liver cells of animals into grape sugar, which is known to disappear in starved animals, are processes of fermentation which unquestionably may count as digestive actions, in so far as they prepare for circulation in the blood or sap the nutritive material stored up in the cells, and so further tissue change. We do not, however, possess equally trustworthy data respecting albuminates and fats, for we can at most regard only as probable the absorption of peptone and its retro-metamorphosis into albumen, described by Hofmeister as effected by the adenoid tissue of the intestinal mucous membrane, though many facts suggest that in this process there enter fermentative decompositions and changes in cell-life.

I hope these few facts will suffice, gentlemen, to give you a general notion of the meaning of the word *digestion*, and to show you that no sharp distinction can be made between the animal and vegetable kingdoms in this respect. It is important to show you now the extraordinary range and great significance of those processes which are concerned in converting the crude organic nutriment into special forms for the use of the cells, and the uniform principle that all these processes are in some manner peculiar. They are in the last instance always fermentative processes, by which Nature is served for this purpose throughout the entire realm of the organic world, and a proper acquaintance with the importance of digestion is directly bound up with a clear and precise knowledge of the importance of fermentative action.

Frankly, in *digestion* we have only to do with the reception

and preparation of organic materials. Plants and animals derive their nutriment from the organic and inorganic world. But the digestion of inorganic matter in the animal economy is only of secondary interest, if we except the very important relations of certain chlorides to the hydrochloric acid of the gastric juice.

We have not now to examine closely the fate of nutriment which has passed into the juices and tissues of the body, and the nearly related but not now in question subject of tissue change, in which assuredly the inorganic matter plays a very important part, but we must learn the necessary preliminary steps, that is, the proceedings by which the organism converts various food stuffs into absorbable material. The great part of this has, however, little to do with inorganic bodies, so that we need devote only a few words to them.

Inorganic bodies are taken in the form of water and salts with the food. Water, the importance of which is too lightly appreciated, although it constitutes 80 per cent. of our tissues, quite independent of the fact that it acts as a medium of solution for the different matters in the exchange between the lumen of the alimentary canal and the vessels, in recent times has received new importance from the part it is shown to play in the fermentative processes going on everywhere. The salts undergo certain decompositions according to their affinities, but otherwise suffer no changes. So far as they are soluble in water and diffusible through animal membrane, they are absorbed, turned to account in the organism, and the remainder passed out with the different excretions. So far as they are not soluble, they pass straight through the alimentary canal, and are able, wherever they may lodge, to give rise to mechanical derangements—as, for example, the little soluble phosphate of magnesia frequently forms the nucleus of an intestinal calculus. It is quite otherwise with organic matter. Besides certain organic acids, such as acetic, malic, lactic, butyric, &c., which so far behave like the inorganic, we can recognise four fundamental types under which we may group the most diverse forms and compounds which make up the chaos of our aliment. But the *albuminates*, *gelatines*, *carbohydrates*, *and fats*, with few exceptions, are not assimilable as such, so that the chief part of the digestive function is the metamorphosis of these into absorbable modifications. The principal means by which the organism performs this duty is by the action

of *ferments*. Only by the changes which albumen, fat, and starch undergo through these ferments does it happen that they can pass from the intestine into the lacteals; without the action of ferments the nutrition and life of the organism would be impossible. Allow me, therefore, first shortly to sketch the doctrine of ferments and the rôle which they play in the animal organism. They have, at the same time, a general interest not limited to digestion alone, inasmuch as, as has been recently especially indicated by Hoppe-Seyler and Nencki, they take part in the *combustion processes* of the organism.

Lavoisier and Laplace founded on their great discoveries the doctrine of *animal heat as a combustion process*, in which the animal gives out as much heat as it can form by combustion of carbon, which may be found as carbonic acid in the expired air; while Magnus's investigations on the different carbonised and oxidised contents of venous and arterial blood localised this combustion process in the capillaries; so the view stood apparently incontrovertible, that the oxygen taken in by the lungs burns the carbon-containing elements of the blood. This process forms in the last instance carbonic acid and water, and, as far as the nitrogenous material is concerned, the products of the so-called retrogressive metamorphosis. This hypothesis seemed so well founded and was so well supported, that, for instance, Liebig believed that on deeper respiration, and consequently increased introduction of oxygen, an immediate increased combustion must ensue, and most physiologists and physicians compared the lungs "to bellows which make a fiercer fire in the forge the more they are blown," notwithstanding the fact that the above quoted investigations of Magnus had shown that the oxidation processes take place not so much in the blood as in the fixed tissues. But in recent times a reaction has taken place against this long dominant explanation. Pflüger and his school have adopted the view that the cells are, in a certain sense, independent, so far as their function is concerned, of the quantity of oxygen introduced into the blood, somewhat as a mill by the damming of the mill-stream must be driven, whether there is more or less water. Then the gas tension of the cells, that is the carbonic acid produced in them by the action of oxygen, increases with their activity, and can, as I have proved, reach its greatest height in fever. The increased taking up of oxygen (Colasanti, Finkler, Lilienfeld) is

also in such cases not the cause but the result. The factors which regulate the intensity of the combustion process lie in the cells, and the degree of oxidation is the expression of their vitality and the consequence of the condition or state of their protoplasm. The carbonic acid, on the other hand, as Hermann has proved in excised frog's muscle, and Pflüger in living cold-blooded animals, is independent of the presence of oxygen in the surrounding air, so long as the tissues retain a store of oxygen, and its production is not to be regarded as a direct oxidation, but rather as a process of dissociation.

If the view is no longer tenable, that the oxidation processes in the cells are a more or less direct result of oxygen taken up by the blood, and the earlier somewhat rough notion of the process of oxidation is corrected, on the other hand, chemical facts are known which do not conform to the view that oxidation only goes on in the blood and tissues. The following facts are of this order: 1. Neither albumen nor fat, under ordinary conditions, as they are present in the blood, can combine with atmospheric oxygen. This occurs only when the oxygen exists as ozone, a body which, as Pflüger, in opposition to A. Schmidt and Huizinga, has shown, has not yet been proved to be present in the blood. If we extract the oxygen out of the blood into a Torricellian vacuum by an air-pump, at the base of which a slip of guaiacum paper is fastened, no blue colouration occurs, as I have convinced myself in two experiments, following Pokrowsky. Moreover, according to Rajewsky, the friction which the blood undergoes in the capillaries is not sufficient to form ozone, as might be suspected from analogous facts. The oxygen circulates in the blood in the form of oxyhæmoglobin, but this is so easily decomposed, and gives up its oxygen to fluids free from oxygen, that the oxidations which appear to take place in the bodies of animals, cannot, according to Hoppe-Seyler, be effected by a solution of oxyhæmoglobin. 2. Certain processes take place in the blood, which cannot be regarded as oxidations but as reductions, such, for example, as the formation of urobilin (hydrobilirubin) from hæmochromogen (the colouring matter of the blood corpuscles), and the formation of hippuric acid out of kinic acid, when this substance is introduced into the blood. 3. Various very easily oxidisable substances, as, for example, pyrogallic acid or pyrocatechin, both derivatives of

benzol, probably pass unchanged through the blood, and are excreted in the urine in the form of dichotomised sulphuric acid. For all that, a solution of pyrogallic acid in an alkaline fluid takes up oxygen, and changes with such extraordinary energy that it is employed for the quantitative estimation of this gas in the atmosphere. 4. There can be no doubt that a part, or perhaps the whole of the albumen which comes into the circulation is not burnt up, but is at first split up into complex bodies, some containing much carbon and hydrogen, others nitrogen, of which only the former are oxidised, the latter being converted by synthesis, or by giving up water, and under certain circumstances carbonic acid into urea. In this way the undoubted conversion of albumen into fat may take place, it being formed from the non-nitrogenous portion of the albumen molecules. E. Baumann thinks he has discovered such a splitting up in urine, where the so-called ether-sulphuric acid appears in the urine as sulphocarbolate of potash. In this case the phenol is split off from the albumen of the food by decomposition in the intestine, and absorbed. Moreover, if we can accept Salkowski's statement that urea may be formed from nascent hydrocyanic acid and water, the former may originate in the splitting of albuminous bodies. We have better evidence of the formation of urea out of ammonia salts (Salkowski, Schmiedeberg, and Hallervorden), and in birds, of uric acid out of ammonia salts (Minkowski), and by v. Schroeder the liver has been shown to be the seat of uric acid formation. So far the general result of these researches has been to show that each molecule of albumen circulating in the organism is not straightway oxidised, but that it undergoes a complicated process of splitting, combining, oxidation and reduction. If we consider these four points, certain comments suggest themselves on the first and second heads. Nothing opposes the supposition that the protein substances, fat, &c., undergo, as the starting-point of the cell activity, a peculiar unknown intramolecular change, which facilitates combustion by the neutral oxygen. As an example of such sudden cell activity, I would quote the play of colours in the pigment cells of many animals, which often depends upon a sudden re-arrangement or change of the cell contents.

On the other hand, both the last points seem to be so important, that I give you the equations according to which these

reduction phenomena occur outside the organism in the presence of reducing substances.

1. The reduction of kinic acid to hippuric acid.

Kinic acid + hydriodic acid = benzoic acid + water + iodine.
$C_7 H_{14} O_6 + 2 HI = C_7 H_6 O_2 + 4 (H_2 O) + I.$

A similar reducing process occurs, in the organism as Meissner, Sheppard, and Stadelmann have shown, whereby instead of hydriodic acid a still unknown reducing action of the intestinal contents takes place, which, in accordance with recent discoveries, we must regard as a phenomenon of bacterial life.

The benzoic acid combines with the glycocoll present in the organism, and forms

Benzoic acid + glycocoll = hippuric acid + water.
$C_7 H_6 O_2 + C_2 H_5 NO_2 = C_9 H_9 NO_3 + H_2 O.$

2. The reduction of the colouring matter of the blood corpuscles, hæmochromogen, into biliary colouring matter and urine colouring matter (bilirubin and urobilin or hydrobilirubin), by the use of nascent hydrogen, a very energetic reducing agent, has been recorded by Hoppe-Seyler. As to the final fate of albumen we know that the cyanogen compounds may very easily represent albumen, or nearly related substances.

According to E. Salkowski, by the action of two cyanide molecules on each other urea is formed as follows:—

Hydrocyanic acid + hydrocyanic acid + water = urea + carbon dioxide.
$CO\ NH \quad CO\ NH \quad H_2 O \quad CON_2 H_4 \quad CO_2.$

Phenomena like the preceding, noticed under 3 and 4, are not reconcilable with the view that the elements of the blood and tissues exclusively support very energetic and rapid oxidising processes. It may, therefore, not seem strange under these circumstances that Hoppe-Seyler observes in support of his theory, as Künkel, on theoretical grounds, and as the result of direct investigations, has lately suggested, that heat is given off in all fermentation processes, and that this may be the source of animal heat. In the second place, in all fermentations atomic hydrogen is given up, and reducing processes go on, whilst in consequence of this nascent oxygen is set free, and assumes the part of an energetic oxidising agent, giving rise to a series of

chemical processes, such as the formation of anhydrides, aldehydes, and higher oxidation stages. As is directly proved by the nature of resulting products in the decomposition of albumen by putrefactive organisms, reduction and oxidation must go on side by side, a process which finds its analogue in numerous chemical reactions, of which I will only instance the destruction of albumen by caustic potash. Here, as there, we have at the same time the products of reduction and oxidation, and indeed, what is very noteworthy, in the case of bacterial putrefaction, without the intervention of the atmospheric oxygen.

As Nencki, in a series of chemical examples, has suggested, it may be that we have a splitting of water into atomic hydrogen (H), and hydroxyl (HO), by which a double action of oxidation and reduction is rendered possible.*

The putrefactive processes are provisionally inseparable from the life of the accompanying organism, and what we call putrefaction is a perfectly definite vital process. It cannot advance our knowledge of the subject to apply putrefactive processes to explain vital processes, as each is, after all, only a special form of vital activity. Nevertheless, we may compare these processes with the object of improving our knowledge, and I believe Hoppe's theory should be accepted in this sense. I will therefore adduce facts which are able to further this object very greatly, and also fall into the category of fermentative processes.

* Such an example is the splitting up of amidocapronic acid or leucin ($C_6H_{13}NO_2$) into valerianate of ammonia ($C_5H_{13}NO_2$), carbonic acid (CO_3H_2), and hydrogen (H_2), by decomposition of water, which may be understood in the following way:—

$$\begin{array}{ccccccc} \text{Amidocapronic acid.} & & & & & & \text{Oxycapronic acid.} \\ CH_2(NH_2) & & \diagdown\underline{H}\diagup & & \text{Ammonia.} & & CH_2(HO) \\ \text{I} & + & HO & = & NH_3 & + & \\ C_5H_9O_2 & & & & & & C_5H_9O_2 \end{array}$$

and:

$$\begin{array}{ccccccc} \text{Oxycapronic acid} & & & & \text{Methylenglycol.} & & \text{Valerianic acid.} \\ CH_2(HO) & + & \diagdown\underline{HO}\diagup & = & CH_2(HO_2) & + & C_5H_{10}O_2 \\ \text{I} & & H & & & & \\ C_5H_9O_2 & & & & & & \end{array}$$

Valerianic acid combines with ammonia to form valerianate of ammonia ($C_5H_{10}O_2—NH_3$). Methylenglycol, an unstable compound, splits into formaldehyde and water, and by taking up hydroxyl and hydrogen forms carbonic acid and hydrogen as follows:—

$$\begin{array}{c} \diagdown\underline{H}\diagup \\ C\quad O \\ \diagup\overline{H}\diagdown \end{array} + \begin{array}{c} \diagdown\underline{H}\diagup \\ HO \end{array} + \begin{array}{c} \underline{HO} \\ \diagup H \diagdown \end{array} = CO_3H_2 + 2(H_2)$$

I shall return to this subject. For the present, it is enough to have drawn your attention to the example of animal heat, which touches one of the greatest and most important questions in the animal economy, on the bearing of our knowledge of fermentations. It is not long since that we included in the area of fermentative actions a definite group of diseases, the so-called infectious or zymotic diseases, and ascribed a direct causal connection to them, so that the typical derangements of the normal course of the vital processes, such as we have in certain pathological processes spreading by "contagion," were regarded as fermentations. A tangible ground for this fermentation theory would be the existence in each infectious disease of a specific micro-organism, which, as the yeast forms carbonic acid out of the surrounding sugar solution, might give rise to a peculiar fermentation in the tissues and juices of the animal body, which would be expressed in the particular pathological process. This view can, however, no longer be held, especially since the important researches of L. Brieger. According to him the action of pathogenic bacteria gives rise not to fermentative processes, but to a poisonous product of tissue metamorphosis of these smallest living things, which gives rise to immediate poisonous action, so that this product is rightly called toxine.*

Brieger could prove that Koch's cholera bacillus, the typhus bacillus of Koch and Eberth, the staphylococcus pyogenes of Rosenbach, and many others, not only gave rise to characteristic decompositions after the manner of putrefactions, but to direct specific products of a poisonous nature prepared from suitable nutrient fluid, which in part corresponded to already known chemical bodies of a very poisonous nature, penta and tetramethylendiamine, methylguanidine, &c., in part to new highly poisonous bases corresponding in type to substituted ammonia. It is to these bodies that Brieger applies the name of *toxines*, and identifies them as *typhotoxine*, *tetanotoxine* (tetanin), &c.

By these investigations for the first time do we obtain some actual knowledge of the specific action of bacteria, and by them a crown is placed on the proud edifice of modern bacteriology, but we are nevertheless obliged to abandon the use of the word zymotic in its old sense, at any rate for infectious diseases. It is at the same time very interesting that in these doctrines, based

* το τοξον sc. φαρμακον was the poison with which the ancients smeared their arrows.

on exact data, the vague speculations of earlier times join hands with the more certain acquisitions of advancing knowledge.

The iatro-chemical school, or its head, Van Helmont, in his Ortus Medicinæ, used promiscuously the terms fermentatio, digestio, putrefactio; Becker thought that combustion and fermentation were analogous processes; Lavoisier compared physiological combustion to the spontaneous burning of dung at lower temperatures; Stevenson derived animal heat from fermentations; and Mitscherlich identified directly life with putrefaction.

The word "ferment" was used by the alchemists of the 14th and 15th centuries in the sense of a force which, without becoming weaker itself, could produce great effects in other masses, a quality which, for example, was sought for in the philosopher's stone. Even in the present day, the definition is current which A. Meyer, a well-known and renowned investigator on this subject, gives in his Chemistry of Fermentation for 1874. It runs thus: "That a number of chemical processes not explicable according to the rule of affinities, owe their occurrence to the presence of certain matter which is not recognisably concerned in the reaction, and the quantity of which stands in inordinately small relation to the magnitude of the chemical processes caused by it." This explanation in part no longer holds good, as we have learnt to regard the majority of fermentative processes as consisting of the splitting up and transposition of water, as above related, but the second part is still correct. But if we keep to the biological standpoint, we may consider it a fact, not quite universal but yet certain, so far as all fermentations in animal bodies are concerned, that fermentations in the presence of water and the ordinary body temperature give rise to extensive chemical processes with the smallest quantity of ferment, processes which without ferments we could only effect by very high temperatures and very energetic oxidising or reducing agents. These processes consist in the decomposition of highly complex compounds into simple molecules with simultaneous increase of water, or, to employ the terms of chemists, *in the hydration of anhydrides*. But this property, which, figuratively speaking, represents in our organism the flame of a Bunsen's burner, which the chemist needs in order to produce similar effects, is that which must make the activity of ferments appear especially important to us.

Six principal properties are common to all ferments: 1. All

ferments belong to organic nature. 2. All ferments act only in the presence of water. 3. The sum of the products contains more hydrogen and oxygen, even in the condition of water, than the original matter. 4. All ferments decompose peroxide of hydrogen. 5. All ferments act best at temperatures between 30° to 60° C. (diastase at 70°). They can endure a temperature of—20° without injury. Paschutin has proved that the specific action of the salivary ferment remains strong up to 55° C. (46° Kjeldahl), but becomes feebler with higher temperatures, and disappears at 73°. Invertin loses its capacity for inversion, according to the researches of A. Mayer, at a temperature between 40° and 50° C. This is only true of watery solutions of ferments; when dried the so-called soluble ferments of the animal body are not so easily destroyed by heat as was believed at one time. Salkowski has shown that pancreatic ferment may be heated for hours to 160° without losing its specific qualities, and similar observations have been made by A. Mayer, Hüppe, and others, respecting other ferments. 6. Every ferment possesses a specific action, and can produce out of one and the same substance a different result according to its nature. So, for example, a solution of sugar is decomposed by yeast into alcohol and carbonic acid, by inversion into grape sugar and fruit sugar, by the bacilli of milk curdling ferment into lactic acid, by butyric acid ferment into butyric acid, carbonic acid, and hydrogen, and so on. The action of ferments on peroxide of hydrogen is very easy to demonstrate. If we place some commercial peroxide of hydrogen in a test-tube over mercury, and add a few milligrammes of yeast, a development of gas follows very rapidly. This gas is formed by the decomposition of peroxide of hydrogen, and is oxygen in which a glowing match bursts into flame. However, this catalytic property belongs not only to the recognised ferments, but to other compounds, *e.g.*, to blood. O. Nasse has observed the destruction of peroxide of hydrogen by many animal organs in different degrees, and refers it to the existence of special and otherwise hypothetical ferments, which effect an important part of the current vital processes in the organs and their elements, the cells. You see how near this view comes to that of Hoppe-Seyler, although reached from another starting-point. On the other hand, it is very interesting that a series of fermentations proceed in the presence of certain substances, in some cases more

strongly, in others more feebly, or are quite prevented, and this action is so manifold according to the kind and concentration of the salts employed, that they are far more physiological than chemical processes, and cannot be expressed by any simple chemical equation. To these belong, according to O. Nasse, Kjeldahl, A. Mayer, and H. Schulz, a number of neutral salts, which have different influences upon different ferments, such as diastase, saliva ferment, pancreas ferment, &c.; and according to Luchsinger, glycerine injected subcutaneously in great quantities hinders the transformation of liver glycogen into sugar, and prevents the occurrence of artificial diabetes (puncture and curare diabetes); and here also belong the studies of Chittenden on the influence of hydrochloric acid on the diastatic action of saliva, which is stopped by very small quantities, 0·0001 to 0·0006 per cent., and increased by larger quantities.

Ferments are the integrated elements of certain vegetable and animal juices and tissues. Their production in a pure condition has extraordinary and hitherto insuperable difficulties, and Hoppe-Seyler has described them shortly "as entirely unknown, quite hypothetical" bodies, which are only known by their actions. But they appear to be allied in their composition to albuminoid bodies. A. Schmidt gives an analysis of the emulsin found in bitter almonds as $C=48·76$, $H=7·13$, $N=14·16$, $S=1·25$, $O=18·70$; whilst non-coagulable albumen, according to Dumas and Cahours, has the composition $C=53·7$, $H=7·1$, $N=15·8$, $O+S=23·6$, $S=1·8$. It must be remarked that Barth gives the composition of invertin and of the enzyme of yeast, which converts cane sugar into invert sugar very differently to the above type, $C=43·9$, $H=8·4$, $N=6·0$, $O=41·7$, and $S=0·63$, and A. Mayer has denied that pure diastase contains any sulphur. The latter is all the more noteworthy, as sulphur is known to be a constant and characteristic compound of all albuminous bodies. On the other hand, Loew discovered in the pancreas a ferment purified as far as possible from dextrine and gum-like bodies, which contained $C=52·7$, $H=7·51$, $N=16·6$, $O+S=23·2$, ash$=1·8$ per cent., and comes very near to the composition of albumen given above. At any rate these data on the composition of ferments show that we still are far from having in them chemically pure and well-defined bodies.

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LECTURE II.

Gentlemen,—The fact that some fermentations result from animal or vegetable juices and extracts, and others from the functional manifestations of living organisms, has, for a long time, led to their division into organised and unorganised, or, what means the same thing, organic and chemical, direct and indirect, ferments. The organised ferments are, so to speak, identical with the specific organic structures which we always meet with wherever we find the specific action, and are intimately bound up with the "life" of these structures. The alcoholic ferment is extinguished so soon as the yeast cell is dead. The unorganised ferments, which recently, according to the example of W. Kühne, would be generally described as *enzymes*, are, once existent, independent of the welfare of the mother substance or of the life of their original producers and bearers. Saliva, gastric juice, pancreatic juice, the extracts of certain seeds, as emulsin, myrosin, &c., remain active after the death of the animal or plant, but it is not important for our present purpose to decide whether these enzymes are ready formed as such in the glandular apparatus concerned, or exist there only in a previous stage, as inactive *zymogens*, which are changed into active enzymes under pressure of physiological action, if this expression may be allowed. Many facts, which have been recently closely debated, speak in favour of the latter view. But it is questionable whether this is an essential difference, or only a defect in our knowledge, which does not permit us—to keep to the same example—to extract an alcoholic ferment from yeast, as we extract the gastric ferment from the stomach.

In fact, many considerations favour the view that "it is not permissible to identify a ferment, that is to say, a chemical body which produces decomposition in the fermenting substance, with the organism in which it is formed" (Hoppe-Seyler); and "nowhere in the whole series of ferment actions does a specially vital process take place, but everywhere only a chemical process."

It is obvious that such an explanation, which regards all ferments from a uniform standpoint as secretions of organisms, and allows no direct part in the ferment action to the cell itself, must greatly facilitate our comprehension of these processes. We may hope, sooner or later, to bring about fermentation without these organisms, as we can do now in the case of the "unorganised" ferments. The distinction between "organised" and "unorganised" ferments would then completely disappear; all ferments would be unorganised, only some more, some less, identified with their carriers. The following considerations support this view: 1. A ferment can be extracted from yeast, which converts lævulose into dextrose, and is called invertin. 2. There is an alcoholic fermentation without anything to do with yeast cells, which at one time were thought to be necessary elements of this process. Lechartier and Bellamy found that chopped up leaves and fruits of phanerogams formed alcohol without yeast when placed in an atmosphere free from oxygen (carbonic acid), and thus confirmed an earlier observation of Pasteur. 3. Under certain conditions yeast undergoes a process of self-fermentation, that is, it forms alcohol and sugar out of its own substance without any solution of sugar. According to Béchamp and Schutzenberger, in this way arise many other products of the fermentation of nitrogenous bodies, leucin, tyrosin, sarcin bases, &c., as if there ensued a splitting up of the protoplasm of the yeast into the ordinary results of the tissue-metamorphosis of albumen. According to Nägeli, this is not so much the action of the essential ferment of the yeast cells, as the effect of pollution by fissiparous fungi which grow at the expense of the dying yeast cells and destroy their substance. 4. Also the circumstance that alcoholic fermentation ceases with the death of the yeast, would be consistent with the existence of a chemical ferment in the yeast, if we admit that the latter is indeed constantly being formed, but in so small a quantity that it is at once used by the fermentation. 5. Some of the fermentative results formed can take place without these latter, by purely chemical means, as for example the conversion of sugar into lactic acid, of alcohol into vinegar, and of urea into carbonate of ammonia. Further, the circumstance that the chemical means are at hand to imitate the action of organised ferments in test-tubes and retorts without their intervention, does not prove that the action of organised ferments must be due to a substance

separable from the life and vital functions of the cell, as in the unorganised ferments, and the observations of Lechartier and Bellamy are capable, as we shall see, of another interpretation.

There are, therefore, a series of characteristic differences between the organised and the unorganised ferments. The organised ferments multiply to a certain extent during their activity; the unorganised do not. The organised ferments are, according to a remarkable discovery of P. Bert, killed by oxygen subjected to the compression of many atmospheres; the unorganised remain uninjured. On the other hand, according to Dumas, borax kills invertin, emulsin, myrosin, and diastase, while it leaves the alcoholic ferments unaffected.* And, finally, all organised ferments require for their origin and the commencement of their activity, as well as for its continuance, the presence of free or combined oxygen; for instance, yeast does so to such a degree that it is able to convert arterial into venous blood; whilst the unorganised ferments, according to Hüfner, can work without any oxygen. The last-named properties do not concern so much the hypothetical ferment as the life of the ferment carrier; but in any case the ferment action comes to an end with the life of the ferment carrier. But this is a point which we are not at present in a position to discuss. We are not yet in a position to separate the substratum, the living organism, from the essence, the actual specific ferment. The distinction between organised and unorganised ferments exists, as Nencki says, not merely *προσ ἡμασ* but *φυσει* (Aristotle). It is the difference between chemical and physiological processes, if for both the same laws hold good. As the yeast decomposes the beer wort into alcohol, carbonic acid, glycerine, and succinic acid, it grows at the same time and forms the elements of its own bodies, cellulose, fat, and probably its special protein. As product of its physiological activity, it secretes invertin, which changes cane sugar into dextrine and lævulose, just as the germinating seeds of a plant form their soluble ferments in order to dissolve the stored up material and to decompose it. There are other experiments known which make the search for such a separation between ferment and ferment carrier appear still more unproductive. The question of the connection of fermentation phenomena

* According to Pasteur the spores of certain ferment fungi resist a pressure of ten to twelve atmospheres. Quoted in the Revue des. scienc. med. t. xi. p. 336.

—understanding in its widest sense the action of an organised element—with the physiology of plants (Sachs, Pfeffer), may be answered in a tolerably precise manner. We will confine ourselves to the carefully studied alcoholic fermentation as the prototype, but remark expressly, that the data given here respecting that fermentation may be properly applied to ordinary putrefaction, or wherever organised ferments are concerned. Fermentation products are, according to this view, the expression of a progressive metamorphosis of organic matter (carbo-hydrates, proteids) by the oxygen of the air imprisoned in the living cells* of the particular ferment excitor. The products of this metamorphosis, by the aid of osmosis, get back from the cells into the surrounding medium. They are also, as Boussingault maintains, in a certain degree the secretion of the cells. This metamorphosis of the cell contents, or a part of them, as, for example, in saccharomycetes which produce alcohol and carbonic acid, is the consequence of one of the self-exhausting processes in the cells, which the vegetable physiologists call "their internal respiration" or "intra-molecular respiration" (Pfeffer). The proximate cause of this is probably the temperature, so that a minimum production of fermentation begins at 0°, reaches its maximum at 40°—50°, and stops altogether at 70°—75°. But fermentation, or rather its products, are not to be detected, so soon as the oxygen of the air has unrestricted entrance to the fermenting mixture. For all that, this intra-molecular respiration persists during unlimited introduction of oxygen. It does not attain to a concrete expression because its products are arrested by the free oxygen, and ultimately burnt to carbonic acid and water. These two processes, temporarily divided, decomposed into their two phases, indicate that the yeast in a solution of sugar, by respiring free oxygen without forming alcohol, uses just as much sugar as it would use in fermentation. On the other hand, the occurrence of alcohol and sugar in the above-related observation of Lechartier and Bellamy, is nothing more than the consequence of the self-exhausting "intra-molecular respiration" in the cells of the fruits and leaves, which we, if I may use the expression, surprise to a certain extent in its intermediate stage when we cut off its necessary oxygen. Under

* Fermenting yeast cells placed in a solution of sugar in distilled water continue for a long time to form alcohol and carbonic acid.

ordinary circumstances we do not observe this formation of alcohol, because it is oxidised further by the free oxygen of the air, and is decomposed into its ultimate products, carbonic acid and water. The followers of the doctrine of chemical ferments may regard this intra-molecular respiration as the consequence of a special chemical ferment contained in the cell, and accept, as M. Traube does for yeast, a special, as yet hypothetical and undemonstrated, alcoholic ferment, to which view the remarkable researches of L. Brieger quoted in the former lecture, give a quite new and highly important support, in so far as quite definite well-characterised chemical changes or decompositions are proved to be the result of pathogenic micro-organisms.

Still the two following facts cannot be reconciled with this view:—

First, it is known that not only yeast becomes useless after a time if it does not get fresh oxygen, but that all ferment-exciting hypho- and schizomycetes are only to a certain degree independent of free oxygen (Buchner) and their growth and their accompanying fermentations are conditioned by it. But there are between the growth of the spores by exclusion of oxygen and the death of phanerogams only quantitative differences, such as exist between the winter sleep of a marmot and the normal tissue metamorphosis of an animal. This is not reconcilable with the properties of unorganised (chemical) ferments, which can carry on their fermentative action unimpaired without oxygen (Hüfner) and within very narrow limits. Secondly, in consequence of Lechartier and Bellamy's observation, we must admit the existence of such a ferment in every cell. Fermentation would be nothing more than "intra-molecular respiration," and we should find ourselves arguing in a circle to which there would be no end. Therefore all tissue metamorphoses, which find their limits with the death of the organism and are dependent upon its existence, as the tissue metamorphoses of the higher plants and animals are dependent upon their lives, and are not capable of being originated apart from the same through their elements, are not to be described as fermentations. "Ferments" in this sense, then, are only the "chemical or unorganised ferments." There are other facts and theories which are not reconcilable with the above definition of all so-called "fermentations."

It will not have escaped your notice, on calling to mind the views that Pflüger has of late expressed on the subject of animal combustion, that this so-called "intra-molecular respiration" is nothing but the process which Pflüger has described as "dissociations-process" in animal cells, that is, a decomposition of a complex molecule into simple ones, or the intra-molecular striking off of small fragments from larger ones. Pflüger recognises in it the peculiar essence of all vital processes, the starting-point of the complicated phenomena which make up the life of the individual.

I am unable to do more than glance superficially at these far-reaching and important relations, and must leave you to decide, so far as you can, from the facts I have brought before you, in one or the other direction, either for the ubiquity of the enzymes, or are disposed to regard the action of the so-called organic ferments as a physiological action dependent upon and inseparable from the life of the cell.*

In the meanwhile let us remain faithful to the very convenient division of ferments into organised and unorganised. All purely physiological fermentations in the animal body are due to unorganised, and all pathological fermentations to organised ferments. To the enzymes belong the amylolytic, saccharifying, peptonising, and fat-splitting ferments. As prototypes of the organised ferments, there is a whole series which all belong to the class of organisms now regarded as fungi, and for the most part are of microscopical dimensions. Here belong, so far as we can observe, yeast (*Saccharomyces cerevisiæ* and other forms), the organisms which cause lactic acid fermentation—according to Huppe there are many, chiefly the *Bacillus acidi lactici* of Lister and Pasteur—the vinegar ferment, *Mycoderma aceti*, the bacilli of butyric acid fermentation, *Bacillus butyricus* and others, and the numerous bacilli, cocci, and vibriones which cause destruction or putrefaction of proteids, of which we find, for example, in the text-book of Flügge no fewer than sixteen different kinds described.

The unorganised ferments are ptyalin in saliva, pepsin in gastric juice, pancreatin or trypsin in pancreatic juice, invertin in the intestinal juice, and a sugar-forming ferment present in fresh bile. These soluble ferments formed in the animal bodies, as already stated, have been recently termed "enzymes." Finally,

* I do not regard intestinal putrefaction as properly a physiological process.

there are the diastatic, inverting, and peptonising ferments in plants, for example in germinating barley, in malt, in many filamentous fungi, in carica papaya, in the already described carnivorous plants, and finally as the products of tissue metamorphosis in certain fungi. It was never doubted that the unorganised ferments are the products of organic bodies, which can prove their genealogy clearly and distinctly, and which at one point are united to the chain of organic life. It is quite otherwise for the organised ferments. The stringent proof that the putrefying or fermenting fluids do not contain organised elements within themselves, but that they are introduced from without, is extraordinarily difficult to produce, and has in the shape of the question of generatio equivoca or abiogenesis, the fundamental significance of which is obvious, occupied the learned world from Needham's time, 1745, to our own day. You know that it is principally being fought out over putrefactive ferments, vibrios and bacteria, but that it applies generally to all organised ferments. The decision of these questions is of the utmost importance to the pathology of digestion, and thereby justifies a short account of them. The entire dispute between the panspermists and heterogenists has always turned upon the fact, that if one side brings forward experiments which prove that under proper regulations no spontaneous development of vibrios and bacteria takes place in a suitable nutritive fluid, the other side maintains that in consequence of these regulations the nutritive fluid has lost its nutritive qualities, and therefore a spontaneous development of ferment is impossible; and, on the other hand, if the others believe they have proved spontaneous development, their opponents maintain that either the originally present germs were not removed or made innocuous, or their entrance during the experiment was not excluded. This is the constantly repeated train of ideas in the works of Schröder, Dusch, Schwann, Helmholtz, Wyman, Bastian, Huizinga, Geschleidlen, and many others, who took their ideas from the famous experiments of Guy Lussac, according to whom the oxygen of the air was the cause of putrefaction. Pasteur first, who in the year 1856 brought forward a series of pioneering observations on ferments and fermentation, "qui ont fait cette question presque la sienne" (Guillaud), succeeded by his numerous able researches in establishing, as it appears to us,

the irrefragable proof of panspermism, the quintessence of which is included in the following points, which were proved by strict experiments:—

1. There are at all times in the atmospheric air germs present which are necessary to the development of vibrios and bacteria, but the quantity varies with the locality. In pure land air and on the tops of mountains they are present, as Cohn, Burdon Sanderson, and Rindfleisch ascertained, in smaller quantities than in the impure air of towns. 2. The nutritive fluids do not, by the manipulation which destroys the contained germs, lose the capacity to take up new germs, and to bear and nourish vibrios, when unheated air is admitted to them. 3. The germs contained in the air or the vibrios themselves are destroyed by the prolonged action of red heat, so that in suitable fluids they are no longer capable of development, whilst they stand temperatures of 120°—130° C. without damage. 4. In nutritive fluids free from ferment, to which air is admitted, the same organic forms are found in 24—48 hours as in open fluids, but an alcoholic fermentation has never been established, although the possibility of this on the part of the fluids is conceded, because the yeast cells are not present in the air in sufficient abundance to cause fermentation in the short time allowed, but in those fluids which rapidly undergo spontaneous fermentation (grape-juice, fruit sugar) they adhere to the surfaces of the vessels used in their manufacture.

These are the fundamental observations from which the following corollary may be drawn, which is of special interest for us practitioners of medicine. If arterial blood, under the necessary precautions, be introduced into a receptacle which was submitted to glowing hot air, and to this blood glowing hot air be admitted, no putrefaction follows, an observation which demonstrates before our very eyes the untenability of the doctrine of a spontaneous putrescence of the blood, the putrid fever of the old writers, which played so great a part in humoral pathology, and even now-a-days springs up here and there. The method of these experiments is so simple and ingenious, that I must explain it in one or two words. Imagine a T tube which is connected at one end with a red-hot tube from a furnace, through which air can come, and the other end with an air-pump, and the third with a somewhat short tube in which is a solid piece of glass. Each division may be shut off from the others by a stop-cock.

In the other opening of the short tube there is hermetically fixed the finely drawn-out and sealed end of a retort, in which, before sealing, the nutritive fluid * was exposed to the necessary temperature for destroying the germs. It is now clear that, with the aid of the air-pump, first the space from the retort to the stop-cock, which goes towards the iron tube, may be made airless and then filled with glowing hot air, which by proper arrangement of the stop-cocks and use of the pump may be at pleasure removed and renewed, until we are sure that all unheated air has been driven out. If now the hard piece of glass in the wide tube be allowed to fall upon the point of the neck of the retort so as to break it, the nutritive fluid will be brought into contact with the heated air, and the result will be the absence of any putrefaction. The variations of this experiment require no further explanation. Here belong also the researches of Cazeneuve and Livon, who found that the excised and tied bladder, if the urine had been experimentally rendered alkaline during the life of the animal, could be kept for a whole day at a temperature of 50° C., without putrefaction or the growth of fungi, provided that no air entered. I myself have long since shown that we can keep pus from an empyema at the body temperature for a week, if we receive it with exclusion of air under recently purified mercury, while the foul-smelling pus of a perityphlitic abscess, which was probably infected from the intestine, very soon under the same conditions was in a state of stinking putrefaction. We formerly said, † it appears to us that these beautiful experiments of Pasteur's decide once for all the doctrine of generatio equivoca, and with that the question of the spontaneous appearance of organised ferments. Since then the champions of spontaneous generation, so far as in a few cases they have ventured forth, have suffered mortal defeat through the victories of bacteriology in other directions. The botanists on the one side, and the bacteriologists under medical discoverers like Klebs, and especially above all others Koch, on the other side, have taught us the methods by which to preserve nutrient bases for an unlimited time, and have furnished us with an intimate knowledge of the conditions of the growth of "organised ferments." Wherever fermentative or putrefactive organ-

* The so-called Pasteur's fluid contains: aq. distil. 100·0, sacch. crystall. 10·0, ammon. tart. 0·2—0·5, pot. phosph. or yeast ash 0·1.

† In the first edition of these Lectures. Berlin, 1879.

isms are present, they are introduced from without, although their extraordinarily wide distribution and the consequent innumerable possibilities make a strict proof of their introduction not always possible. All recent experimental data concur in this, that without the entrance of *organised ferments* no putrefaction takes place. The opposite experiments have proved to be erroneous, *and up to the present time not a single putrefactive process has been proved to occur without the intervention of living cells—sprouting or fissiparous fungi.*

In the preceding lecture I have told you that one aspect of fermentative action may be defined after A. Mayer, as that "their amount stands in an extraordinarily small relation to the extent of the resulting chemical processes." At the same time this relation has its limits, and it must not be understood that with unlimited growth on the one side there could be equivalent decrease on the other. Theoretically, yes! But practically not, because in all careful studies of fermentative actions it has been proved that the accumulated products of conversion after a certain time inhibit the fermentation, and this happens in proportion to the rapidity of action and quantity of the ferment. Moreover, within the time that the ferment retains its unimpaired activity, it appears to be a universal law that the amount of products of conversion is proportionate to the amount of the ferment, and consequently the time within which the conversion of a definite quantity of fermentable material takes place is inversely proportional to the quantity of ferment employed (Roberts, Ellenberger, and Hofmeister).

We have already spoken of a cardinal factor of fermentation, namely, that it occurs by taking up water. On the intimate nature and mode, how and in what part of the molecule it occurs, the following important table from Hoppe-Seyler indicates. But, above all, you will obtain from it an insight into the different fermentations, so far as they interest us, and with its help you will be able easily to discover your whereabouts in the future. It may be observed that the following formulæ are in many instances not exact, but only approximate expressions of the changes that take place in fermentations. According to the suggestions which were made by Nencki on the bases of the processes which occur in the decomposition of albumen by caustic potash, the processes of fermentation run their course in a much

more complicated way than this table shows. The formation of lactic acid out of grape sugar, for example, is only possible by the taking up and giving off of water and the formation of a non-existable intermediate product dioxypropionaldehyde (CH_2 $(OH)—CH (OH)—COH$), and further by the assistance of water and peroxide of hydrogen.

But we should gain nothing by pursuing this purely speculative discussion on their construction, so that we pass it by. At the same time the following formulæ express not so much the actual relations as an approximate illustration of them, so far as it is possible to put together in a table all the concurrent reactions of separate fermentations. Thus, for example, in the conversion of starch there is formed maltose, a body nearly related to grape sugar, with the formula $C_{11} H_{22} O_{11} + H_2 O$; in alcoholic fermentation glycerine and succinic acid are formed, as well as traces of vinegar, as bye-products. But it is in accordance with the best authorities not to introduce them in the formulæ. We have already spoken (p. 14, et seq.) of the other factors, so that I may avoid their repetition, and can pass on now to what is more strictly our subject.

Process of Fermentation.

1. Conversion of anhydrides into hydrates.

Ptyalin	Starch or glycogen to dextrine and grape sugar. $2 (C_6 H_{10} O_5) + H_2 O = C_6 H_{10} O_5 + C_6 H_{12} O_6$
Diastatic Enzyme of Pancreas	Starch to maltose and dextrine. $3 (C_6 H_{10} O_5) + H_2 O = C_{12} H_{22} O_{11} + C_6 H_{10} O_5$
Invertin	Cane sugar to lævulose and grape sugar (dextrose). $C_{12} H_{22} O_{11} + H_2 O = C_6 H_{12} O_6 + C_6 H_{12} O_6$
Emulsin	Amygdalin to grape sugar, oil of bitter almonds. $C_{20} H_{27} NO_{11} + 2 (H_2 O) = 2 (C_6 H_{12} O_6) + C_7 H_6 O +$ hydrocyanic acid. H C N.
Pepsin Pancreatin (Trypsin)	Albumen + n ($H_2 O$)= Pepton Leucin Tyrosin Asparaginic acid Glutamines, &c.
Pancreatic ferment, breaking up fats.	Tristearin to glycerine and stearic acid. $C_{57} H_{110} O_6 + 3 (H_2 O) = C_3 H_8 O_3 + 3 (C_{18} H_{36} O_2)$
Urea decomposition by micrococcus ureæ.	Urea Carbonate of ammonia. $CH_4 N_2 O + 2 H_2 O = CO_3 (NH_4) 2$

Butyric acid fermentation by bacillus subtilis.	Lactic acid $2 (C_3 H_6 O_3) + 2 (H_2 O) =$ Butyric acid + carbonic acid and hydrogen. $C_4 H_8 O_2 + 2 (CO_3 H_2) + H_4$
Putrefactive processes, the ferments of which have not yet been isolated.	Hippuric acid to glycocoll and benzoic acid. $C_9 H_9 NO_3 + H_2 O = C_2 H_5 NO_2 + C_7 H_6 O_2$ Taurocholic acid to taurin and cholic acid. $C_{26} H_{45} NSO_7 + H_2 O = C_2 H_7 NSO_3 + C_{24} H_{40} O_5$ Cellulose to carbonic acid and marsh gas. $n (C_6 H_{10} O_5) + n (H_2 O) = 3n (CO_2) + 3n (CH_4)$ Albumen + n $(H_2 O)$ to globulin, peptone, &c.

Leucin and other Amidic acids
Tyrosin
Indol, Phenol, Scatol
Fatty acids
Carbonic acid
Ammonia
Sulphuretted hydrogen.

2. Conversion with passage of oxygen from hydrogen to carbonic acid atoms.

Alcoholic fermentation.

Yeast.	Grape sugar to alcohol and carbonic acid. $C_6 H_{12} O_6 + 2 (H_2 O) = 2 (C_2 H_6 O) + 2 (CO_3 H_2)$.
Bacterium lacticum (Cohn)	Milk sugar to grape sugar to lactic acid. $C_{12} H_{22} O_{11} + H_2 O = 2 (C_6 H_{12} O_6) = 4 (C_3 H_6 O_3)$.
Mucous or Mannite fermentation by microc. viscosus.	Dextrose. Gum. Mannite. $15 (C_6 H_{12} O_6) = 3 (C_{12} H_{20} O_{10}) + 16 (C_6 H_{14} O_6) +$ $3 (CO_2) + 3 (H_2 O)$.

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LECTURE III.

Gentlemen,—From the simple sac-like invagination of the asteridea, into which the "moving ocean" drives the food of the animal, up to the complicated gastro-intestinal system of the ruminants, with their three stomachs, the intestinal tract and its appendages fulfil the needs of each animal species in a wonderful manner. This is strikingly expressed, amongst other things, by the relation of its length to the length of the body. It is, on easily understood grounds, largest in the ruminants, as 15—20 : 1 (in the sheep 28 : 1); in the carnivora as 4 : 1, and midway between these stands man with 6 : 1.* Swammerdam has shown that the tadpole, which lives on plants, has an intestinal canal about nine times the length of its body, whilst in the frog, which lives on animal food, the relative length falls to 2 : 1. Interesting, though probably without profound significance, is the observation of Beneke, that the intestinal canal in children is not greatly longer in proportion to the length of their bodies than in adults.

That the digestive tube in the higher animals also is merely an invagination of the surface of the body, is suggested by the prolongation of the epithelium of the epidermis into its oral and aboral openings; but it stops there, and there is another kind of epithelial layer where the special work of digestion begins. If, however, as we have already (Lecture I.) shown, the intestinal tract is constructed on one and the same type throughout all classes of the animal kingdom, the above-mentioned appendages, which prepare the digestive juices (so far one can regard the stomach as a sac-like appendage of the intestine), are not so uniformly distributed. They are present equally in all vertebrata, with the exception of the pancreas, which is absent in many fishes; and this fact should have impressed

* But we must remember that the length of a man is measured from his heels to his vertex, while in most animals we measure from the end of the head to extremity of the caudal vertebræ, so that we might get very different results if a uniform plan were adopted.

on our predecessors that a principal and fundamental distinction between herbivora and carnivora, corresponding to the nature of the digestible matter, does not exist. On the other hand, stomach, liver, pancreas, &c., are absent, sometimes singly, sometimes entirely, in the invertebrata, conditions which cannot be gone into now, although it is extraordinarily interesting to follow the gradual formation and development of these structures, as the growing requirements of nutrition demand them. We shall restrict ourselves to the vertebrata, and will keep well within our prescribed limits, so that we shall pass over the details of the topographical and coarse anatomy of the various organs, and only concern ourselves with their functions. Yet we shall have something to say of their minuter structure, so far as this may be necessary to the understanding of their function.*

Food and drink are generally taken, apart from some exceptional cases, by the mouth. We drink, that is, we bring the narrow cleft of the mouth to the edge of the vessel and to the surface of the contained fluid, and exercise a sucking action with the lips and cheeks. We in this way draw the drink into the cavity of the mouth and then transmit it by the act of swallowing onwards, first into the back part of the mouth cavity (the pharynx), and then through the œsophagus into the stomach. Food, so far as it is not previously divided and comminuted, is bitten or minced by the incisor and canine teeth, and ground and torn up into finer particles by the molars, towards which the portion of food lying on the back of the tongue is pressed by that organ. This action, mastication, is performed by the muscles connecting the upper and lower jaws, by pressing the latter in a horizontal and vertical direction against the former. The masseter and temporal muscles draw up the lower jaw against the upper, the internal pterygoids draw it upwards and forwards, the external pterygoids forwards, while it is drawn downwards by the digastrics, the mylo- and genio-hyoids. Finally, the buccinators force back between the teeth such portions of food as escape laterally between the upper jaw and the cheeks.

The teeth are the assistants of the stomach, whose work they

* See F. W. Krukenberg, Grundzüge einer vergleichenden Physiologie des Verdauung. 1882, Heidelberg. Winter's Verlag.

facilitate or even render possible. Bad and defective teeth have not only the consequence of making digestion more difficult, as they insufficiently prepare the material, but they occasion many pathological accidents, such as putrefactive processes, which develop in the carious teeth, and are transplanted from the cavity of the mouth to the stomach. The care and maintenance of the teeth is, therefore, a very important factor of good digestion, too long neglected by us in Germany; and the expression of an English author, that the treatment of stomach diseases begins with the teeth, has in it much that is true. It is true that now-a-days we do generally take care to have carious teeth stopped, defects replaced, and such faults are not suffered in the younger generation. But the proper prophylaxis, that is, the careful purifying of the mouth by washing it many times a day, and especially after meals, and brushing the teeth with a disinfecting mouth-wash, is not yet very common.

Food during the act of mastication is saturated with the secretion of the mouth, the mixed saliva, and coated and lubricated by it. Mastication causes reflexly an active secretion of the gland structures concerned.

We will begin with the Salivary Glands.

Of the four gland groups, the united secretions of which formed the *mixed saliva*, we will first take the submaxillary glands, not only because the classical investigations of C. Ludwig and Cl. Bernard discovered in them an apparently inexhaustible field of fruitful physiological investigations, but also because in them the processes of glandular activity, κατ' ἐξοχην, are most instructively studied, and the fundamental data for the theories of the secretion of glandular organs have been derived from them. Do not be surprised, therefore, if we occupy an apparently disproportionate amount of our time on the study of the submaxillary glands.

The submaxillary glands belong to the type of mucous glands, that is, they secrete a fluid rich in mucus but without diastatic action, and they are distinguished thereby from another group of glands, which were named "albumen glands" (serous glands), by Heidenhain, whose secretion more resembles the composition of blood serum, but contains a large amount of albumen, and above all, at least in many cases, a diastatic ferment.

Both groups belong in essential features to the acinous, or as they have been recently called, the compound tubular glands, and in both the distribution of blood and lymph vessels and their structural arrangements are on the same plan. The blood vessels ramify in a delicate network over the acini, and are separated by the alveolar wall from the lymph spaces, which are more or less full, according to the physiological condition of the gland, and the capillaries are thereby separated more or less from the wall of the acinus. They unite in spaces between the gland lobules, finally opening into the lymph vessels of the hilus. The interacinous connective tissue offers no special peculiarities. In its meshes are found lymph corpuscles and Waldeyer's plasma cells.

The minute structure of these glands has been studied, especially in the dog, rabbit, cat, calf, and sheep, and their anatomy is known completely. A number, mostly 5—10, of epithelial cells group themselves round the commencement of the excretory duct, which lies in the middle, and are surrounded by a common capsule, the membrana propria. The latter is a structureless membrane, stretched between peculiar connective tissue-like cells with rib-like processes, so-called basket cells (Henle, Boll), and cuts the cells off from one another and so shapes the alveolus. Each alveolus is attached to the duct like a raspberry to its stalk; the latter is covered with a special very finely striated-looking epithelium (Pflüger). Under ordinary circumstances, as for instance when the animal employed has not lost an unusual amount of saliva before the gland was removed, the special gland-cells contain two zones, best seen in alcohol preparations, less distinctly in fresh sections —an outer granular layer, containing flattened nuclei, protoplasmic and lying against the membrana propria, and a glass-like mucous inner zone, turned towards the commencement of the excretory duct, which in extent surpasses the first. The hyaline contents of these last may with certainty be proved to be mucus, or probably an earlier stage of mucin, mucigen, by the appropriate micro-chemical re-agents (cloudiness on adding acetic acid, clearing again with strong mineral acids or weak alkalies. According to Watney, hæmatoxylin stains mucigen but not mucin). The entire outer zone has its nuclei easily stained with colouring agents (carmine, hæmatoxylin, &c.)

the inner remains unstained. In many alveoli, especially frequent in the gland of the sheep, much more rarely in the dog, some of the cells are smaller than the others, and contain only protoplasm. They lie close under the membrana propria, and bend the other cells into a sickle-shape, so that Gianuzzi has described these complexes of cells as "crescents" (halbmöndchen). Heidenhain believes that they represent an early stage of the others. If the gland is irritated, either reflexly from the mucous membrane of the mouth, or directly from the nerves by electrical stimulation, or indirectly by pilocarpine injection, so as to continue secreting for an hour or more, we find, as Heidenhain discovered, a quite changed appearance in the gland prepared in exactly the same way, and which moreover feels harder than an unstimulated specimen even when fresh, but especially after hardening in alcohol. The alveoli are all smaller, the interalveolar connective tissue is more distinct. Nothing is to be seen of the hyaline inner zone of cells; they are filled with brightly-stained protoplasm; the nucleus is pushed up to the middle, is large and round; the distinction between the "crescents" and the rest of the alveolus has disappeared. While a stained section of the unstimulated gland looks clear on account of the preponderance of the unstained mucus, the sections of the stimulated gland present a universal, vivid colouration from the staining agent employed, as you may perceive in these two preparations stained with hæmatoxylin; in short, there is such an enormous difference between the stimulated and unstimulated gland, that it never could be guessed that both were derived from the same organ. The passage from one to the other condition may be observed in all the intermediate stages of the gradual disappearance of the mucus and the recoil of the protoplasm. There can be no doubt that in the "mucous glands," as well as in the "albumen glands," about to be described, the protoplasm of the cells is converted by their function into the specific secretion or a preliminary stage of it, and this is effected not at the moment of secretion but during the functional pause of the organ, or as we should rather say, during the period of its lessened activity. A complete cessation of secretion within the cells in all these glands, so far as we know, never takes place.

We can by no means admit, as the sequel will show, the

earlier simple view, that the cells of the active gland merely afford an outlet to a separated, and as such, previously formed secretion. The function is rather the formation during secretion from the cell contents of a definite specific secretion out of a material prepared and stored up during the pauses in secretion. The submaxillary gland converts mucigen into mucin, the stomach propepsin into pepsin, the pancreas protrypsin into trypsin, &c. In the "albumen glands" the cells are not destroyed but have the power of self-regeneration. With respect to the mucous glands, the fate of the cells has been for long discussed and is still a subject of controversy.

According to Heidenhain, the original cells are completely disorganised by their protoplasm becoming mucus, and in the "stimulated" gland we have before us only the young after-growth of the "crescents" as a consequence of a trophic "nerve-action." I formerly sought to prove that the cells persist and only lose their mucus, and that one can obtain the appearance of a stimulated gland without physiological stimulation by withdrawing the mucus from the cells in another way, namely, by treating these fresh sections with feebly ammoniacal carmine solution. Heidenhain holds, however, that the resemblance of preparations artificially deprived of mucus to the physiologically exhausted gland is only apparent, and states that he and his pupils, Lavdovski and Beyer, have directly observed (in the sublingual gland) the disappearance of the mucous cells and their formation from the parietal cells, while he refers to the analogy of the processes in the so-called mucous cells of the external skin or of the lower animals, the total mucous transformation of which is recognised. Langley, on the basis of more recent investigations, interprets the "young" cells of Heidenhain as only old altered mucous cells, and does not admit that the "crescents" disappear after prolonged secretion, but that they only grow smaller and their nuclei more distinct. Knüppel was able, at least in insects, to prove the destruction of the secreting cells. After repeating my experiments, I can confirm the observations first made by me in 1869, and I have the satisfaction that such well-known microscopists as Ranvier, Bizzozero, Dewitz, and Stöhr, have come to the same conclusion in other ways. The question appears to me to have been much advanced by a very interesting investigation of Arloing and Renaut,

based upon the elective staining properties of the cells. If we stain the cells of an unstimulated gland hardened in osmic acid and alcohol, by means of hæmatoxylin-eosin, the mucous cells become pale blue, the parietal cells red, and the nuclei dark violet. If the mucous cells of the stimulated gland are destroyed and are replaced by the growth of the outer zone, it must at least be possible to show by the staining that there is a displacement in the arrangement of the cells. But this is not the case. The mucous cells remain blue, though much diminished in size; the cells of the crescent are red, and Arloing and Renaut conclude therefrom "que les cellules muqueuses de la gland sous-maxillaire ne se detruisent pas en fonctionnant." I must leave these gentlemen the responsibility for their observation, which I have not had the opportunity to confirm; but I hold the proposition as still correct with which eleven years ago I ended these remarks in the first edition of this work: "The destruction of individual cells and their restoration by an immediate new formation during the relatively short period of stimulation seems to me still doubtful." It should be noticed that this proposition does not exclude the possibility of the events described by Heidenhain taking place under very excessive irritation. But so far as physiology enables us to determine what takes place normally, it must be an abnormal, that is in a certain sense a pathological condition in which they can occur. I will only add that I had the opportunity to investigate the salivary glands of a newly-born puppy, which I show you here to-day, and which, as Heidenhain has stated, have throughout the appearance of stimulated glands. But this young animal had never formed any saliva to fill the cells and displace their protoplasm. We shall return to this point later on in speaking of the pancreas.

The secretion of the glands is excited through nerve filaments, which run in part in the chorda tympani, in part in the sympathetic, and influence the gland parenchyma, not continuously but periodically. Their terminal branches have been traced by Pflüger, in a work published in 1869, up to the individual gland cells; he considers the salivary cell directly "as a swelling on a medullated nerve," and "the gland cells as budding outgrowths of the nerves," so that he in this fashion makes the most intimate continuity between the nerve and cell. But none of the numerous

followers of Pflüger—and there is scarcely a histologist, says Heidenhain, who has not had a longing to confirm his important statements—has been in a position to confirm his descriptions; and Pflüger appears to Heidenhain, in consequence, to be under a delusion, his multipolar ganglion cells being merely the anastomosing cells of the membrana propria. At all events, the gland obeys the nerve as a good horse his rider, and nothing is so surprising as to see how drop after drop flows from the canula fastened in the excretory duct when one of the above nerves is excited. By means of electricity the gland may be made to secrete for hours, even for a whole day, if care is taken by the use of a weak current and short pauses not to exhaust the nerve and gland-parenchyma too early. It is known that at the same time the temperature of the gland rises as much as one-and-a-half degree of the Centigrade scale, that the blood stream is hastened, that the venous blood escapes of an arterial colour; the pressure in the salivary duct when connected with a manometer rises higher than the pressure in the gland artery, and a pure, aqueous, slightly fibrin-forming secretion is poured out. Only the first few drops of the secretion are made turbid by epithelium and other elements of the tissues—products of the irritation of the duct by the canula—as well as by crystals of oxalate of lime, which are separated during the stagnation in the duct. Pure saliva is free from morphological elements. All this applies only to the secretion obtained by exciting the chorda, the "chorda saliva." The "sympathetic saliva" is thicker, jelly-like, much richer in mucus, is secreted in much smaller quantity, and instead of widening there occurs a narrowing of the vessels and slowing of the blood-stream. If acids or alkalis are injected into the duct (Gianuzzi), or the animal is poisoned by injecting atropin into the circulation (Heidenhain), and the chorda be then stimulated, no secretion follows, but the vessels become dilated, and red blood flows out of the divided veins. (For this purpose a large dog requires 8—10 milligrammes of sulphate of atropia.) *There must, therefore, be two sets of fibres in the chorda, one quickening the circulation, the other increasing secretion*, or these latter fibres, or their peripheral organs, the cells, may be paralysed by the said injections. If, whilst the gland is under the influence of these poisons, the sympathetic be stimulated, the ordinary sympathetic

secretion is obtained. The cells are therefore capable of acting, and consequently the chorda nerves must be paralysed, and thence it follows that the chorda and sympathetic fibres run separately up to their terminations, and have different points of connection with the gland cells.

The known antagonism between atropin and eserin suggests the experiment to obviate the action of atropin poisoning by injecting a requisite dose of extract of physostigma, and this is, in fact, possible. If salivation is induced in an animal by injection of pilocarpin, and then atropin be given, the flow of saliva ceases. But after the injection of the requisite dose of eserin the saliva begins again to flow from the canula spontaneously, or after a small dose of pilocarpin. These beautiful results of a series of experiments of Heidenhain's are not only of importance for the salivary glands, but bear, as it is scarcely necessary to insist upon, a universal significance. It is being shown daily that apparently uniform nerve fibres included in a common sheath possess not a uniform, but a very different action on the peripheral organs. I refer to the sciatic; and, by the above observations, Heidenhain has given us another exceptionally clear instance of this condition. I shall be able to show you the experiment, which is not difficult to perform, and which I have already repeated many times. At the same time, you can observe the salivating property of hydrochlorate of pilocarpin, which we can employ instead of the electric current. The action of pilocarpin is paralysed by atropin, and this again by eserin.

The constituents of the normal chorda saliva are approximately as follow: the absolute figures cannot be given here or elsewhere.

Water	996·04		
Solid residue.........	3·96—of which		
		Inorganic	2·45
		Organic	1·51

The organic constituents are: mucin, which is precipitated as a whitish or fibrinous cloud when I let fall a drop of saliva into a test-tube of water acidulated with acetic acid; traces of albumen, proved by a slight cloudiness on boiling, the xanthoprotein reaction (boiled with nitric acid it forms a beautiful orange

red colour on adding ammonia), and the test with ferrocyanide of potassium and acetic acid (a white precipitate). The submaxillary saliva contains no diastatic ferment, as Heidenhain, Grützner, and Zweifel have proved (the last in newly-born children). The saccharifying action repeatedly observed by myself and others after its action on starch for an hour or more, is common to all albuminous bodies, which at a certain temperature by decomposition form traces of ferment, and cannot be regarded as a specific action of the secretion. The organic constituents are chloride of sodium, chloride of potassium, carbonate and phosphate of lime, phosphate of magnesia, and phosphate of soda. The sympathetic saliva is richer in mucin, poorer in water, and has, therefore, a much higher percentage of organic constituents than the chorda saliva. The solid constituents of the saliva diminish with the duration of the stimulation—the organic more than the inorganic (Ludwig)—and rise with the strength of the nerve irritation. Lastly, on the condition that the water and inorganic salts increase *pari passu* with the strength of the stimulus, the organic constituents increase at first more rapidly than the salts, but after the lapse of a certain time they decrease as the gland gets exhausted. If the stimulus is diminished, the quantity of salts in the secretion begins to be diminished, and they decrease more rapidly than the organic matter, so that their total excretion becomes less than the latter; in one case the organic constituents are surpassed by the inorganic, and in the other case they are more persistent; both quantities are to a certain degree independent of one another, or, in other words, *the quantity of organic matter is not only conditioned by the strength and the duration of the stimulus, but also by the state of the gland* (Heidenhain).

These are very complicated conditions, which we want to make as clear as possible, because, as we shall see directly, they afford a very significant point of departure for the theory of secretion.

Finally, there are gases in the saliva, free carbonic acid and nitrogen. If the duct be tied, considerable œdema of the gland occurs. The so-called "paralytic" saliva is the secretion of saliva which sometimes occurs after section of the nerve, and often continues for days, and which, discovered by Bernard,

has never been explained, either by himself or by his followers. A young investigator in the realm of secretion, N. Langley of Cambridge, holds the paralytic saliva to be a consequence of an increased irritability of the central nervous system consequent upon the operation, transmitted to the gland through the sympathetic instead of through the divided chorda. It is possible by anæsthesia and by inducing a condition of apnœa to lower this irritability, and by causing dyspnœa to increase it, so that the paralytic secretion can be increased or diminished by the means described.

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LECTURE IV.

Gentlemen,—The remarkable discoveries to which the thorough investigation of the submaxillary glands has led, demand a somewhat deeper acquaintance with an organ so specially interesting for many reasons. The description of the other salivary glands may, nay must, be short, because we know but little about them.

The parotid is absent in birds, because it is the masticatory gland κατ' ἐξοχην, and grows in the animal series in proportion to the development of the masticatory apparatus. Its *histological* conditions are very similar to those of the submaxillary, but there is no mucus in its cells. They consist of a clear ground substance with a granular protoplasm sparingly distributed in the form of a reticulum (Klein); their angular mesially placed nuclei take up colouring matter readily, while the rest of the cell is only slightly stained. Here, as before, a change in the microscopical structure occurs on stimulating the nerve, with this difference, that it is brought about, not by irritating the cerebral nerves, but the sympathetic. The cells shrink, become very cloudy; their protoplasm is better stained by carmine; the round, many-nucleolated nuclei become very distinct. This apparent difference of nerve action in the submaxillary on the one hand and the parotid on the other will in truth prove to be an analogy, so soon as we have shown more completely the influence of the nerves on the glands. The special glandular nerve is the auriculo-temporalis, which unites with the small superficial petrosal nerve at the otic ganglion; the latter is connected with the glossopharyngeal through the ramus tympanicus (N. Jacobsonii), and so conveys reflexes from the cavity of the mouth to the gland. Heidenhain, whom we have again to thank for our exact knowledge of details, stimulated the nerve from the tympanum. Moreover, the gland may be stimulated from the sympathetic. In this case also the circulatory conditions are, as in the submaxillary, dilatation of vessels and quickening of the blood-stream on stimulating the cerebral nerve; with narrowing

of the vessels and slowing of the blood-stream on stimulating the sympathetic. Here also the pressure (118 m.m. mercury) of the secretion in the duct may be made by continuous stimulation much higher than the blood pressure. Moreover, there is in this gland a notable relation between the irritation of the sympathetic and cerebral nerves. The irritation of Jacobson's nerve only, for instance, gives an aqueous secretion free from mucus, which contains a little albumen, paraglobulin, a diastatic ferment, and the usual salts. The total of solid constituents in this secretion is small, and of these the organic are less than the inorganic. The irritation of the sympathetic is followed generally by no secretion. But if the nerve of Jacobson and the sympathetic are stimulated at the same time by two electrodes, the secretion not only becomes richer in solid constituents, but the relations between organic and inorganic are so upset that the organic preponderates. For instance:

	Solids.	Salts.	Organ. matter.
N. Jacobs. alone	=0·56	0·31	0·24
N. Jacobs. + sympathet.	=2·42	0·36	2·06

This suggests that the basis of this relation may be sought for in the contracting effect of the sympathetic on the vessels. But apart from the fact that the quantity of salts in both cases is approximately equal, that during simultaneous stimulus of both nerves being rather the greater, this idea is directly disproved by the observation that tying the carotid has no influence on the experiment, although this would produce much greater interference with the circulation than stimulation of the sympathetic. We must also admit that the cerebral nerve presides mainly over the excretion of water and salts, the sympathetic governing the passage of organic matter into the secretion by the formation of soluble substances in the cells. When we learn, too, that similar changes in the contents of the secretion, in salts and organic constituents, follow the duration and intensity of the secretion as in the submaxillary, and that the contents of the secretion in organic matter stand in no direct relation to the quantity of water which the gland secretes, we cannot avoid the conclusion that the sympathetic nerve exerts a specific "trophic" influence on the gland cells. The nerve of Jacobson governs mainly the separation of water, while the sympathetic

presides over the formation of the specific elements of the secretion. For the same reasons we were obliged to admit the existence of two kinds of nerve fibres in the chorda, water-secreting and mucus-secreting nerves, only they ran together in one nerve sheath, while they go separately to the parotid. This explains why the change in microscopic structure, which consists chiefly in the changes in the organic gland substance, in one case is brought about by stimulus of the sympathetic, in the other of the chorda. If I first irritate the cervical sympathetic of this rabbit with a canula placed in Stenson's duct according to Heidenhain's method, until I have obtained about 1 cm. of secretion, and then invoke the cerebral nerves by injecting pilocarpine into the veins, and collect the same quantity of secretion, you see that the sympathetic secretion becomes a jelly-like coagulum by heating, while the cerebral secretion becomes only feebly turbid, although both looked equally clear before, a proof of the richness of the sympathetic secretion in albumen. From the above data we may derive the fundamental and significant information that in these organs, and probably in all similar glands, there are *two sorts of nerve fibres possessing the power of controlling secretion; these are secreting and trophic nerve fibres running in the same sheaths or separately.* The former influence the circulation of the glands and effect the secretion of water, salts, and small quantities of albumen. The latter cause the secretion of the specific secretion, namely, greater quantities of albumen, mucus, and ferment; indeed, according to Ellenberger and Hofmeister, the parotid secretion contains more ferment than that of any other salivary gland.

It might appear, as indeed we stated in the second edition of this work, that the mixed secretion was compounded in a definite and satisfactory manner.

But Langley's recent observations have shown, as we may say, unfortunately, that the relations are not nearly so clear as, according to the original observations of Heidenhain, they seemed to be.

The English physiologist has clearly proved the inhibiting influence of atropine injection on the secretion of the chorda saliva. But he has also studied the composition of the product of bilateral stimulation of the sympathetic and chorda after atropine poisoning had taken place. He found no great difference from that of simple stimulation of the sympathetic, but on

investigating the secretion at other times under complex conditions, as, for example, under different intensities of electrical stimulation, after dyspnœa, compression of the aorta, venesection, intra-venous injection of salt solution, &c., he came to the conclusion that the secretion is influenced variously under varying conditions so far as concerns each of the three factors of which it is composed, viz., water, salts, and organic matter. Consequently we must distinguish not only two but three kinds of secretory nerves, presiding respectively over water, organic matter, and salts.

Langley thinks it is not necessary to accept such a complicated and quite hypothetical mechanism, but he believes, basing his belief on the facts already stated, that the chorda after atropine poisoning is paralysed in its secretory and trophic (hypothetical) fibres, without doing violence to the facts, and consistently with the far simpler hypothesis *that only one kind of nerve fibre exists*, which exhibits different functions according to the changing condition of the gland cells.

In man, a fine silver canula may be easily introduced, as I show you here, into Stenson's duct, and a copious secretion takes place, chiefly by reflex action. This secretion is alkaline, but, according to Astaschewsky and Mossler, with moderate secretion, or when fasting it is feebly acid, free from mucin, and has a diastatic action. In diabetics, though not invariably, it contains sugar, which is sometimes so abundant that its presence can be proved by fermentation, reduction, and polarisation.

We know little about the *sublingual gland*, which is formed on a very similar type to the submaxillary. It furnishes a secretion similar to but more viscid than the last, which may contain as much as 2·7 per cent. of solids, and is controlled by nerves which run in the trunks of the chorda and sympathetic. We owe our principal knowledge on this subject to some researches carried out by Beyer in Heidenhain's laboratory, in which he tried to prove that on strong stimulation the destroyed mucous cells were replaced by a growth from the parietal cells, and for that purpose the whole of the acini are filled with small highly granular cells, but on moderate stimulation as well the destruction of the mucous cells and the preformation of the new replacing cells from the parietal cells may be followed. I refer with respect to these relations to the descriptions already given

(Lecture III., p. 34, et seq.), and especially to the work of Stöhr, "Ueber Schleimdrüsen," for as they are much the same in the parotid as in the sublingual we may conveniently abstain from a detailed recapitulation.

The secretion of the *buccal and labial glands*, likewise acinous glands, may be obtained pure only after tying all the other ducts. But the significance of such an experiment does not repay the trouble involved, as the difference between the mixed oral saliva and the secretions of the particular glands already described, shows that the glandulæ buccales et labiales separate a mucous secretion very like that of the other glands. The product of all the secretions poured out into the oral cavity forms the mixed or oral saliva, the origin of which from various sources has been already referred to. It falls from out of the cavity of the cleansed opened and somewhat lowered mouth, sometimes in clear drops, sometimes drawing long threads of mucus after it, according as it is derived more from the mucous or the albumen fluids of the oral cavity.

Its composition, according to Hammerbacher, is:—

Water	994·203
Solids	5·797
containing—	
Epithelium and mucin	2·20
Ptyalin and albumen	1·40
Inorganic salts	2·21
Potassium sulpho-cyanide	0·04

Its sp. gr. is from 1004—1009, but these limits may be transgressed in both directions; according to Wright, a specific gravity of 1017 was found in a case of exclusive meat diet.

The reaction is ordinarily feebly alkaline during or soon after eating, but it may often be neutral to litmus paper, as I have often shown in fresh human saliva; during fasting and in many pathological conditions, *e.g.*, in fever and in diabetes, it is at times acid. This depends upon an acid fermentation of matters present in the mouth at the same time, or perhaps upon the above-mentioned property of the parotid saliva to become acid under certain conditions. A remarkable but not constant constituent of mixed human saliva is sulpho-cyanide of potassium, an alkaline compound of sulpho-cyanic acid, CNSH, which

may be recognised by its red colouration with ferric chloride, and appears to be especially present in the parotid secretion. Why this sulpho-cyanide of potassium is sometimes present and sometimes absent, and in what relation it stands to pathological processes, we are ignorant. Its amount apparently varies, but seems to average about 0·014 per cent. (J. Munk). Formerly this sulpho-cyanide, the presence of which was quite unintelligible, was regarded as a decomposition product, probably, according to Pettenkofer, formed from urea and potassium sulphide. Since what we have learnt of the destruction of albumen in the organism has made the formation of hydro-cyanic acid in the highest degree probable, the presence of sulpho-cyanic acid has become more intelligible, though it still remains very extraordinary, according to Ellenberger and Hofmeister, that the saliva of the horse, ox, sheep, and pig contains none. Incidentally I may mention the morphological elements of the mixed saliva, namely, salivary corpuscles distinguished by their active molecular movements, and abraded epithelial scales. Pure saliva, according to the above-named investigator, is free from micro-organisms, although they are found in the mixed saliva of the oral cavity; perhaps this is why the mixed saliva has a stronger amylolytic action than any of the component salivas separately. Finally, a fact is stated by many authors which may be easily verified, that an important saccharifying agency is derived from the leucocytes which find their way into the fluids of the mouth from the follicles of the tongue and tonsils, though it may be that without the assistance of micro-organisms they would be powerless.

But this amylolytic action which is brought about by the diastatic enzyme of the saliva, the so-called ptyalin, is of great significance for the mouth and stomach digestion, and deserves a closer description. We have not succeeded in obtaining pure ptyalin. As is so frequently the case in fermentation processes, we conclude from the known action of the secretion the presence of a ferment to which we have given a name, but have not yet obtained in all its purity. It is Cohnheim's merit to have first obtained a diastatic and approximately pure preparation from human saliva. A most simply performed experiment teaches how rapidly and energetically mixed saliva converts starch into maltose and sugar. Solera found traces of "grape sugar" twelve

seconds after the commencement of the reaction, but probably the process begins even more quickly. I have treated a solution of starch with saliva and sufficient hydrochloric acid to inhibit the diastatic action of the ptyalin, warmed it to 37°, then added rapidly a previously measured neutralising amount of alkali, and at once boiled some with Fehling. A decided reduction took place. Yet a considerable time is always needed, varying according to the relations between the saliva and the amount of starch, at the temperature of the body always many hours, before all traces of starch have disappeared from such a mixture. The starch is first converted into a soluble form, then into the intermediate products, actroodextrine and erythrodextrine, two bodies nearly related to starch, finally into a kind of sugar called maltose, as well as small quantities, about 1 per cent. (Musculus, v. Mering) of grape sugar, a process which, according to Paschutin, takes place most rapidly in boiled starch paste at 38°—41° C., and according to the observations of E. Pfeiffer and O. Nasse, by adding sodium chloride. This may be increased to a maximum of 3·9 per cent., while by sodium carbonate it is diminished. In a 2 per cent. solution of boiled starch, which had remained thirty minutes in the fasting stomach of a healthy person, I found only various dextrines and maltose, but no trace of grape sugar.

Simply as we have given the process of converting starch into sugar in the table at the end of Lecture II., it is not really so, the processes in question taking place not successively, but in part at the same time; still we may regard the table as expressing the truth in a convenient form. We know, too, that the old view that starch is changed into sugar by the action of the saliva, is so far erroneous that grape sugar is only present in traces, as opposed to the formation of dextrine and maltose. But this is not of great importance for the question of digestion, as the important fact is the change of insoluble into soluble hydrocarbons. Mixed saliva changes starch into sugar not only in alkaline and neutral, but also in acid solutions, if the acidity does not exceed a certain point, which is for hydrochloric acid between 0·01 per cent. and 0·025 per cent., and for the organic acids is distinctly higher, up to 3 per cent. On the other hand, a very small amount of acid, not exceeding 0·0001 to 0·0006 per cent. of free HCl. according to Chittenden, increases the activity of

ptyalin. The food passes through the mouth so quickly, that there can be scarcely any question of the occurrence there of an extensive chemical action, and besides the greater part of the saliva is swallowed; so with respect to the special evolution of its diastatic function, it signifies very much how the relations shape themselves in the stomach, to which we shall return in the proper place. Ellenberger and Hofmeister have observed in the horse that the saliva first secreted converts starch strongly, the latter does so feebly or not at all, so that there must be a previous preparation of ferment in the gland during the intervals of secretion, as it evidently cannot be formed *pari passu* with the demand. Ptyalin appears to possess, like other ferments, a certain power of resistance to the influence of various digestive juices and processes of tissue metamorphosis, so that it may be transported to the kidneys and excreted in the urine. Cohnheim discovered a diastatic ferment in the urine; Grutzsser, Bolovtschiner, and others have further followed the passage of ferments into the urine, and shown that the reducing power of the urine after the addition of starch is strongest after meals, while the urine after fasting passed in the morning contains only small quantities. It therefore remains a question whether in truth we have to do with a diastatic ferment, ptyalin, or whether in urine, and other transudates of the body, substances are present which convert the starch into reducing substances but not into sugar, and should not be described properly as ptyalin. The earlier investigations are not sufficiently definite, and Brensing could not prove, on careful experimentation under fixed conditions, that there was a true sugar formation from starch either in urine or in its alcoholic precipitate product. The starch disappeared, reducing substances made their appearance, but no sugar.

Like all alkaline fluids, the saliva, that is, mucous mixed saliva, forms with rancid fats (that is, fats which contain some fatty acids) beautiful emulsions on shaking, better, according to Ellenberger and Hofmeister, than can be obtained with pig's or sheep's bile. A second very important property of the saliva is to lubricate the morsels of food. The following observation of Cl. Bernard's, demonstrating this very clearly, is little known and is worth relating. The œsophagus of a horse was opened, and boli of moist oats were given by the mouth, which every 1—1½ seconds came out of the opening, so that in nine minutes 500

grms. had passed. But when the parotid ducts were cut, the parotid secretion, and therewith the chief part of the saliva, being made to flow externally, the boli appeared only every 1—2½ minutes—in 25 minutes only 360 grms., which gives a difference per minute of 41·1 grms. At the same time it was noticed that during drinking, the secretion of the parotid (and probably also of the other glands) ceased entirely. Of course the food is mixed with a greater amount of saliva in proportion as it is rough and dry, so that Ellenberger and Hofmeister found in the horse that double the quantity was secreted for oats, and four times as much for hay, as compared with half the weight of damp grass. In accordance with this, or in consequence if you like, is the fact that the salivary glands throughout the animal kingdom are feebly developed in proportion to the wateriness of the food of the animal, be it, that the water is taken in or with the food (aquatic animals).

Tuczek estimated by a special method how much saliva was taken up by a well-masticated and afterwards expectorated morsel of food, and found, as was to be expected *a priori*, that the poorer the food was in water the more saliva was secreted. In this way there were secreted daily, with black bread 545 grms., with white bread 698, with mixed diet 476, with bread and potatoes 659, with highly albuminous diet 773 grms. of saliva. The quantity of saliva for 24 hours is estimated by Bidder and Schmidt to be in man 1,500 grms., but as has just been shown there must be great variations according to the quantity and quality of the food. Both sides of the oral cavity do not share equally in this work of secretion. Pflüger found that a third more was secreted on the masticating side than on the other. The secretion of saliva takes place reflexly through the glosso-pharyngeal and lingual nerves, the food exercising the necessary mechanical, thermal, or chemical stimulus. The reflex centre is in the nucleus of the facial nerve on the medulla oblongata, and a cerebral centre exists in the region of the crucial sulcus (Eulenburg and Landois and others) which sends fibres through the internal capsule to the spinal centre. Bechterew saw, after the application of a feeble faradic current to the superior anterior part of the fissure of Sylvius, a copious secretion of saliva. Moreover, the stimulus to the secretion of saliva which follows certain odours or even psychical impressions, is reflex, and likewise, in

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part, through the trigeminus. The secretion follows, as we have seen, immediately upon the stimulus, and if Schofield saw, in a parotid fistula, secretion begin first a minute and a half after eating, it is probable that there was a pathological cause for this protraction. If I pass a fine canula, as above described, into Steno's duct, a few seconds after the inhalation of ether vapour the first drops flow from the canula. In the same way, as Schofield states, by pepper and salt, chloroform, ethereal oils, acids, and the like, the flow of saliva may be excited from the gastric mucous membrane; indeed even from distant nerves, such as the sciatic, we may induce secretion of the submaxillary glands, and it is no uncommon phenomenon to observe increased salivation from intestinal worms. Injections of pilocarpine, as Ellenberger and Hofmeister state, make the secretion watery and impair its diastatic action.

What influence the suppression of the entire salivary secretion has on the general health cannot be stated, because such cases, with the exception of the local and transient diminution of saliva in fever, in many cases of poisoning, &c., are not known. Undoubtedly we sometimes meet with neurasthenic persons whose chief complaint is of "unbearable dryness of the mouth," but in such cases the secretion of saliva is by no means suppressed, it is only diminished. Zweifel has found the diastatic action of the parotid unchanged in the diseases of children. The loss of saliva through fistulous openings does not appear to have any particular consequences, although an English author, Wright, who collected for purposes of observation 250 grms. of his saliva in one week, lost 11 pounds weight (?).

On the other hand, the pathological increase in the secretion of saliva does not permit its consequences to be distinguished from those of the original affection, but if we may judge from the cases of ptyalism in hysteria, paralysis, &c., it may continue for a long time without injury to the health; on the other hand, where the copiously-secreted saliva is swallowed and the stomach digestion checked, digestive disturbances with their consequences may occur. Finally, as a curiosity, may be mentioned the cases of intermittent sialorrhœa, which, according to Rayer, are described as recurring about every 30—50 days. From the phosphate and carbonate of lime in the saliva, which become partly decomposed and combined with organic matter (mucin, albumen,

fungi), arises the formation of salivary calculus, and the plugging of the salivary duct, with its consequences.

I cannot leave the subject of the salivary glands without referring to a view which Heidenhain has expressed with reference to an old view of Hering's on the process of secretion. When you remember the remarkable condition, that the pressure in the salivary duct is higher than the blood pressure; when you think of the fact that the poisoned cells of the submaxillary gland stimulated from the chorda, in spite of the quickened circulation, do not secrete, while there is neither œdema of the gland nor increased flow of lymph, you will agree that the blood pressure cannot explain the process of secretion, and that the immediate cause must lie in the cells themselves, and not in the stimulating influence of the blood. We may fully admit that the circulation is only concerned so far that it delivers the raw material, and meets an increased demand by an increased rapidity of the current. Hering held secretion in the salivary glands to be a process similar to the osmotic processes in plants, having its origin in the capacity of mucin for taking up water. He thus explained the fact that the salivary pressure is higher than the blood pressure, because it is known that extraordinarily high hydrostatic pressures are produced by osmotic actions. But this is refuted, amongst other things, by the circumstance that, as we have seen, in the parotid secretion, which is free from mucin, a similar high pressure occurs. One must ascribe this capacity of imbibition not only to the mucin, but also to the entire glandular protoplasm, which absorbs water out of the lymph vessels and blood in proportion to its hypothetical imbibing capacity, so that once for all the cell contents stand under a higher pressure than the blood. But these to a certain extent *compressed* cell contents cannot flow out towards the duct before the stimulus of the glandular nerves indicates that the ordinary opposing forces are removed. Whether one should attribute this, with Heidenhain, to a molecular arrangement, or imagine a thermal influence which only concerns a part of the cell, and in this way permits a definitely directed osmotic current, remains uncertain. In short, this explanation concerns only the water and salts. The understanding of these processes is assisted by the observations of Stricker, if they should prove true, that the secretion of the cutaneous glands of frogs results from an

active contraction of the cells. The organic matter, we have seen, is in a measure independent of the quantity of water secreted, and its quantity increases with the stimulus. Here comes in a peculiar function of the cell contents in the production of the specific elements of the secretion. Perhaps the following factor finds its place here, in addition to the so-called trophic nerve stimulus: Kühne and Lea have proved directly, in the case of the pancreas, that all parts of a secreting gland are not functionally active at the same time. Pathological facts, for example in the kidneys, show that all parts of a gland are not at all times equally active in secreting. If one part of the gland cells is active longer than the other, and consequently is in another stage of its work, perhaps it becomes early very exhausted, and thus differences can arise in the combined secretion during the different phases of the stimulus, which would explain Heidenhain's facts.

Similar remarks of a general nature upon the process of glandular functions which we have brought forward with reference to the salivary glands, are applicable to the other glandular organs—for example, the gastric glands, the pancreas, Brunner's glands, &c. They gain, therefore, a general significance for the comprehension of these mysterious and wonderful secreting processes, so that equipped with these views we need not return to this question.

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LECTURE V.

Gentlemen,—Our conceptions of the transmission of the food prepared in the mouth, and the fluid taken up by it, onwards to the stomach, were formerly relatively simple. By the action of the proper muscles the morsel was propelled into the pharynx, the entrances being closed to the nasal cavity by the palate, to the air-passages by the glottis and to the anterior part of the mouth, and the swallowed mass propelled downwards by the peristaltic contraction of the muscles of the pharynx and œsophagus. This description, which was supported by the fact that in many animals, the horse for example, we can see the wave of muscular contraction from the exterior of the neck, was taught by Magendie and strongly held by Heuermann, the physiologist and physician of the last century, and has since, with little modification, been adopted by all authors.

To the labours of Kronecker, Falk, and Meltzer we owe a series of new facts, which lead us to quite another conception of the act of swallowing.

Partly by means of manometric estimation of the pressure in the pharynx, partly by means of œsophageal tubes, which were introduced different distances into the œsophagus, they succeeded in analysing the different stages of the act of swallowing. With this object the lower opening of the tube was provided with a little inflatable india-rubber ball, and the other hand furnished with a Marey's capsule. When the ball reached the desired part of the œsophagus it was inflated so as to touch the walls of the passage, and both by the passage of food and by the contraction of the œsophageal muscles slight pressure was experienced. Any active pressure on the air in the ball was conveyed through the closed system to the index of the Marey's capsule, and could be recorded on the rotating drum of the kymographion.

A similarly arranged ball was at the same time placed in the pharynx, and its indications on the beginning of the act of swallowing were inscribed by the index pen on the drum, so that all the data for measuring the consecutive course of the movements of swallowing were obtained.

It was found that the swallowed matter—fluid or gruel-like—in less than 0·1 second after the beginning of swallowing reached the cardia, and in fact, as Kronecker believes, by the combined action of the muscles of the root of the tongue, namely, the mylohyoids and hypoglossi, it is squirted straight through the œsophagus, so that the bolus of food, by the pressure of the tongue against the hard palate, is put under high pressure as by a piston. This pressure, according to Falk's measurement, in the opened œsophagus amounts to about 20 cm. of water, and under natural conditions must be greatly increased. It is therefore no wonder that it is possible to swallow even standing on one's head. With this chief action, or rather after it, the muscles of the pharynx and œsophagus come into play, and bring about a wave of contraction which divides the œsophagus into three sections, of which each contracts in its own sphere at about the same time. In the first section, which extends downwards about 6 cm. from the entrance to the gullet, the wave begins 1·2 seconds after the commencement of swallowing, in the second (to 16 cm. downwards) after 3 seconds, and in the last just after 6 seconds. Between the contraction of the mylohyoidei and that of the constrictors of the pharynx there is an interval of 0·3 second, and from this to the beginning of the contraction of the first section of the œsophagus 1·2, less 0·3=0·9 second elapse. It follows, therefore, that the pauses which occur between the various phases of contraction, namely, 0·3, 0·9, 1·3, and 3·0 seconds, follow a definite law, and form an arithmetical series with the constant factor 0·3 second. This might seem curious, if it were not shown by the following circumstance to be of great significance. When, for example, one, two, or more acts of swallowing follow at intervals, the smaller the ascertained pauses are for each section of the œsophagus, for example less than 1·2 second for the first section, just so long will the contractions of this and all lower sections be inhibited, and they recur after the last act of swallowing so as to constitute with it only one act. There is also a reflex (?) inhibition with each excitation of the upper section affecting all the lower ones, so that the passage remains open for the bolus to pass. But it appears that this only facilitates the act and is not what renders it possible, as it can be proved that the bolus can be forced through the contracted portion of the œsophagus, and that the action of

the mylohyoidei can overcome the resistance opposed to it. It is an interesting fact that in hiccup a wave of contraction runs, as one would not expect *a priori*, from *above downwards* along the œsophagus.

On reaching the cardia this contraction ceases. The sphincter of the mouth of the stomach rests in a state of moderate contraction, which ordinarily cuts off the stomach from the œsophagus, but appears to yield to repeated acts of swallowing, and gives admission to the cavity of the stomach.

Does the bolus of food stop, that is, does the mass propelled by a single act of swallowing rest before reaching the stomach, or does it go direct to the cardia, that is, as we have seen, in 0·1 second? Kronecker and Meltzer are, partly from direct and partly from indirect observations, in favour of the first view. It is possible by auscultation to follow indirectly the passage of the bolus. After the act of swallowing there occurs a peculiar murmur or sound over the stomach, which was first described by Natanson in 1864, but not carefully studied, and was later described fully by Zenker, and finally by Meltzer, to whom at least belongs the credit of having made the observation more generally known. Apart from the sound produced in the pharynx at the first moment of swallowing, which is transmitted into the œsophagus, and is to be heard throughout its entire course, there are two sounds separated by an interval audible over the region of the cardia, and best heard at the angle of the ribs. First, immediately after the beginning of the act of swallowing, there is a "projection murmur," so called because it has the character of a hiss, as if the fluid were projected straight into the stethoscope. Some time after, in most cases after 6 to 7 seconds, there occurs a second murmur, or rather a complex of rapidly following sounds, which are at times gurgling or clucking, at others trickling or splashing, giving the impression, but by no means without exception, as Meltzer thinks, of air or fluid forced through a sphincter, whence it is called an "expulsive murmur." It seems to me better to describe the murmurs without prejudice as "first" and "second." The first murmur is only seldom heard, and is, where it occurs, caused by relaxation of the cardia and the direct entrance of the bolus into the stomach; the second is constant or nearly so, but is exceptionally absent when the first is present. From the

congruence in time of the latter with the contraction of the deepest section of the œsophagus, and from the rarity of the former taken into connection with the circumstance that it is generally alone and not followed by a second murmur, Kronecker and Meltzer conclude that ordinarily the bolus stops before reaching the stomach, and the second murmur is the resultant of its entrance into the stomach, by, as above described, the contraction of the last section of the œsophagus. In opposition to the view of Zenker, who attributes the second murmur to air forced through the cardia, Kronecker holds that the bolus throws the cardia into audible vibrations, which are strengthened by the resonance of the air-containing stomach. This is not possible. I have observed a number of facts, which have been corroborated in their most important points in a careful dissertation by Dr. Dirksen, which are not in accordance with the explanation given by Kronecker and Meltzer. The chief of these are the occurrence of the typical second murmur without a previous act of swallowing, the typical occurrence in certain persons of a first and second murmur after a single act of swallowing, the frequently very considerable retardation of the second sound to 17 and 20 seconds, and finally the artificial production of the same by intra-ventricular muscular excitement by means of the galvanic current. Moreover, I have convinced myself with certainty that in excised and suitably suspended preparations of the œsophagus and stomach with artificial closure of the cardia, the injection of water never causes a murmur, but the injection of air is followed by an exquisite typical second sound, that is, a series of bursting bubbles; in the first case, on the contrary, one hears a typical first sound, in fact, a true expulsive murmur. Finally, it is possible in the living subject, by prolonged insufflation of air into the deepest section of the œsophagus, to produce a distinct second sound; on the other hand, the second sound may be prevented if care is taken to swallow only fluid without air.

Finally, I have done what Kronecker and Meltzer omitted, that is, I have followed the movements of the œsophageal muscles with the air-ball while auscultating at the same time, and I found, while confirming the careful statements of Kronecker and Meltzer, that, 1. Muscular contractions occur without sounds; 2. Sounds occur without contractions; 3. Sounds and contractions occur without evident swallowing movements,

and these sounds are evidently to a certain extent independent of the passage of the bolus into the stomach.

From all this it follows that the second sound arises not from the vibrations of the sphincter of the cardia and the inflowing fluid, but, as Zenker formerly stated, by means of the air driven in. Quincke came to quite the same results by means of observations on a dog, whose stomach, however, was opened. This investigator thus expresses himself: "That for the production of the swallowing murmur the swallowed matter must contain air." Either the swallowing murmur is the immediate consequence of the contraction of the lowest section of the œsophagus after the commencement of the act of swallowing, though it appears about 6 to 7 seconds later, or it comes later, often without any previous act of swallowing, and is then only to be explained by contraction of the œsophagus or stomach, which occurs from some other stimulus than an evident act of swallowing, or, at all events, without propelling any swallowed material through the cardia. The circumstance depends, too, as Quincke has shown, to some extent on the consistence of the swallowed material, as it occurs with water more easily than with thick fluids, such as gruel, and it depends for its character upon the degree and nature of the fulness of the stomach.

Much more important, in my opinion, are the direct observations of Kronecker upon the retarded passage of swallowed matter into the stomach. He was able, in a man, to palpate the cardia with his finger introduced into the stomach through a fistula, and to feel that nearly 6 seconds after a drink of water the fluid forced open the cardia and entered the stomach. This may be experimentally determined on dogs after opening the stomach, as has been corroborated by Quincke. But it may be objected to these observations and researches that they were made under abnormal conditions, and that at any rate they are valid only for that particular act of swallowing and not for ordinary conditions of feeding; otherwise there must be in every man an œsophageal diverticulum, a sort of fore-stomach, such as is found in some insects, for the accumulation of swallowed material in front of the stomach must cause, as a necessary consequence, dilatation of the lowest section of the œsophagus.

But, gentlemen, I have taken up too much of your time with this digression, as the swallowing murmurs of the stomach have

hardly yet obtained any practical significance, except that their prolonged and repeatedly observed absence indicates occlusion or considerable narrowing of the œsophagus. A very great number of patients were examined by me last year without result as to the value of the swallowing murmur in diagnosis, and Dr. Dirksen came to the same result in his before-mentioned investigations.

At any rate the œsophagus has shown us the way to the

Stomach,

whose functions it is our next business to discuss.

Formerly we distinguished two forms of gastric glands, both tube-shaped, of which one occupies the fundus, and is lined with rounded nucleated cells, the so-called peptic glands (Frerichs); the other is situated in the pyloric portion, and is lined with a more cylindrical epithelium, the mucus glands. The former produce the well-known gastric juice, the pepsin; the latter, mucus. In addition, some observers have found acinous glands (Donders, Frey). Meanwhile, this simple explanation has undergone an important extension by the simultaneous publications of Rollet and Heidenhain. The structure of the gastric mucous membrane, as one may easily ascertain, is the following: the more or less convoluted surface of the mucous membrane turned towards the stomach lumen, appears under low powers thickly covered with numerous crowded pores, the openings of the deep-lying gland tubules, and is invested with a tall columnar epithelium, which extends into the entrances of the gland tubules. In this epithelium there takes place, according to Stöhr, a peculiar mucous transformation of its contents, quite analogous to that by which in the mucous cells of the salivary glands the granular protoplasmic contents are converted into hyaline mucous matter, which distends the cell and pushes the remainder of the protoplasm and the previously central nucleus over to the periphery. When the portion of cell membrane turned towards the stomach cavity bursts, the mucus runs out, and the protoplasm and nucleus take the empty cell, and form out of it a new basal membrane, and the game begins anew. Here, too, by the protoplasm being displaced laterally, structures or appearances are produced similar to the "crescents" of the salivary glands. In a similar fashion Toldt expresses himself, though deviating a little from Heidenhain, who lays great stress

on certain differences in reaction, and thinks that the cells are not bounded by a membrane at their bases, but are open like cornets. Moreover, the strength of this layer of epithelium, that is, the limitation of it to the necks of the tubular glands, varies very much in different parts of the stomach. In the pyloric region the cylindrical epithelium is equal to half the depth of mucous coat, in other parts only from one-tenth to one-eighth of it, so that in the region of the pylorus we find in an equal superficial area fewer glands but more epithelium than elsewhere. In general, several gland tubules have a common excretory duct, so that according to Toldt, in a girl of ten, with 16,971,360 glands, there are only 2,828,560 openings; and in a man of thirty, the relation is 25,179,000 to 6,790,700. Between or below the epithelium lie other, apparently membraneless, cellular elements, which were described by Ebstein as compensatory cells (Ersatzzellen). Also some examples of the about to be described parietal cells (Belegzelle) are here met with. In these, which have, like the salivary glands, a membrana propria strewn with stellate connective tissue cells, we can distinguish an upper, smaller part, the gland neck, and a lower, somewhat wider part, the fundus of the gland. In the neck the cells are placed in a single row on the membrana propria; in the fundus they are numerous, and fill it out like stones in a bag. The cells are pushed together in the middle of the tube, and leave no distinct lumen to be recognised, but it is doubtless present and is sometimes easily seen. If we stain alcohol-preserved preparations with aniline dyes—Heidenhain employs aniline blue, Stintzing recommends recently congo-red for the human mucous membrane—or with hæmatoxylin-chromate of potash after Heidenhain-Sachs, one sees—particularly well in the dog and pig, indistinctly, after one has learnt their disposition in those animals, in man—in a longitudinal section of the glands of the fundus, that the "neck cells" for the most part are brightly stained, large, and have distinctly outlined nuclei, and in many places push out the membrana propria. In the gland fundus, on the other hand, we find smaller cells with distinctly coloured nuclei and granular unstained protoplasm, which are here and there replaced by a cell of the first-named sort, but which still preponderate in quantity and form the principal elements. Sections which have divided the gland neck vertically to the

long axis of the tubule show a crown of regular, rigid, large, darkly-tinged cells, whilst sections of the fundus show an irregularly grouped quantity of uncoloured smaller cells, which are only here and there varied by a large, coloured, roundly-projecting cell placed on the membrana propria. The former are visible distinctly, the latter indistinctly; the former are few in number, the latter are relatively crowded and form the principal elements. Rollet distinguishes them as delomorphic and adelomorphic; Heidenhain, as parietal (Beleg) and central (Haupt) cells. Nussbaum has seen a rare third kind of cell lying between the cells in the pyloric region, in preparations treated with perosmic acid. They are somewhat conical in form, seated with their broad bases on the tunica propria, while their small, rather clear apices extend to the lumen of the gland. According to Sachs, they are to be distinguished from the parietal cells by their clear staining with hæmatoxylin, while the latter, as above stated, become dark, almost black, yet they are very much alike, and by many authors (Stöhr, Dukes) are regarded as identical. Between the tubules rises a sometimes greatly developed support of connective tissue, interspersed with lymphoid cells in the upper part, which exhibits a retiform structure in brushed-out sections. With it are organic muscular fibres, while the vessels of the sub-mucous trunks pass between the tubuli and form a narrow capillary network around the orifices of the glands. In the sub-mucous tissue impinging on the fundus of the gland, I have described in man typical acinous glands without any recognisable excretory duct. Ebstein has undertaken a thorough investigation of the peptic and mucus glands of the pyloric region with reference to the above-mentioned description, and found that the pyloric glands have almost no parietal cells, but an epithelium, very similar to the central cells of the fundus glands, which behave themselves during digestion in a manner analogous to that which we shall immediately describe in the fundus glands. Accordingly, the stomach is divided into two regions, which are already externally distinguished by the colour of the mucous membrane. A pale pyloric portion, with few deep folds and a reddish yellow or reddish grey portion at the fundus and the curvatures, which exhibits an abundant irregular network of folds. Between the two lies an intermediate zone, which varies in extent.

If we trace the influence which the process of digestion and the function of the glands exercise on their structure, we find this at its acme somewhere about the fourth hour after the ingestion of food; the tubes, as Frerichs already described, being swollen out, the central cells very cloudy, swollen, and (in stained preparations) coloured, the parietal cells still larger and more prominent than ever. These striking changes in the cells recede in the last hours of digestion, in which the distended tubes shrink, but the strong colouring of the central cells remains a longer time, until it gives way to the normal condition. We see that, first, at the height of the digestive activity of the stomach, obviously more goes into than comes out of the cells, or they could not swell; and, secondly, their contents must be distinguished from those of the fasting state, or they could not exercise such a much greater absorbing power on the colouring matter of the staining agent. What the nature of this change may be, which in all probability represents the first stage of the special secretion, our pioneer (Heidenhain) has left unsettled. At a certain period of digestion, the parietal and central cells must look very much alike; and I place before you preparations from the dog in full digestion, in which I can find no difference between the two kinds of cells, whilst the distinctions between the two kinds in the preparations from the fasting dog are very noticeable. The question might well be asked, whether the central and parietal cells are originally distinct cells, or only developmental stages, if it were not, as we shall see later on, that they perform quite distinct functions. Edinger had already put forward a similar, but according to Heidenhain and Stöhr, groundless view, and Toldt holds on the basis of a careful, in part embryological study of the subject, that during the entire period of development the delomorphic cells originate from the adelomorphic by increasing in size and successive growth of the granules of the cell body which colour vividly with eosine and perosmic acid. He regards the entire process as a regeneration, independent of secretion, leading within greater spaces of time to a gradual renewal of the cells.

The influence of the nervous system on the stomach was till recently unknown, except that the innervation must run in the trunks of the sympathetic and vagus. We know now very little more, except that by peripheral irritation of the vagus we can

give rise to irregular contractions of the stomach; the same results follow reflexes from the central nervous system, in particular from the medulla oblongata, whether the reflex excitement be central or whether it be of peripheral origin, also in pathological instances, in the one case of injuries and diseases of the brain and spinal cord, in the other of irritation of the mucous or serous membranes, the sense organs (taste, hearing), dreams, &c. All more intimate knowledge of the glandular innervation is wanting. The statements of Cl. Bernard and Frerichs, that section of the vagi is followed by interference with the secreting functions, have been long ago contradicted, and we stand face to face with the bare fact that mechanical irritation of the gastric mucous membrane, whether by ingesta or otherwise, gives rise to hyperæmic reddening with copious secretion; whilst fasting stomachs, as I maintain with Hoppe-Seyler, and in opposition to many recent statements (Rosin, Schreiber, and others), contain no secretion, but only a little mucus. But at any rate, there is a difference between the process of secretion set up by circumscribed chemical, thermal, or mechanical stimuli of the mucous membrane, and that caused by ordinary ingesta or absorbable substances of another kind (peptone, albumoses). The latter action is generally diffused over the whole mucous membrane, while the former is limited to the stimulated spot, and, moreover, may be obtained after section of all the nerves leading to the stomach, and is transmitted either by the nervous apparatus seated in the stomach, or results from the direct stimulation of the gland cells without the intervention of any nervous structures. The secretion of gastric juice occurs not only reflexly through certain sensory impressions, but by simple mental conceptions, and such stimuli may act reflexly from the mucous membrane of the mouth through the channels of the vagi and sympathetic. Richet has proved this to be true in man, in a case with complete fibrous stricture of the œsophagus, where a gastric fistula had been made, and in whom it was shown that when the patient took into his mouth and masticated strongly-flavoured substances, such as citron peel, sugar, and the like, a strong secretion of gastric juice occurred. If, moreover, the following observation of Regnard and Loye be correct, the often disputed direct influence of vagus stimulation appears at any rate to be admitted.

The authors in question stimulated the vagus of a decapitated criminal forty-five minutes after the execution of the sentence, and saw not only movements of the stomach and intestine down to the transverse colon, as well as folding and wrinkling of the intestinal mucous membrane, but also observed numerous drops of gastric juice pouring out over the whole surface of the mucous membrane of the stomach. However, it is by no means proved, first, that they had to do with active gastric juice; and, second, that if it were, it was not merely a squeezing out of the previously existing gland contents through the contraction of the wall of the stomach,—a simple mechanical action instead of a real secretion.

A contribution to the comprehension of the movements of the stomach has been recently made by Goltz. If we expose in a special manner the stomach and œsophagus of two vertically-hanging curarised frogs, so that they can be well observed, and drop a dilute watery solution of salt into both their mouths, after having previously destroyed the brain and spinal cord of one, the following occurs: the stomach and œsophagus of the normal frog are widely distended, full of fluid, quite motionless, only traversed by a to-and-fro peristaltic wave, and look like a blown-up pig's bladder. The œsophagus and stomach of the frog deprived of its brain are empty, and beaded in many places by sharp muscular contractions, which run peristaltically from above downwards. The same occurs when the vagi are cut, whilst electrical stimulation of these nerves only causes slight contraction. This experiment, which may be extended by exciting reflex movements, is easily performed, and, as you see, is of striking significance. In fact, one can conceive no greater contrast than the stomachs of the two animals, especially as it increases with time; for the parts concerned in the frog deprived of its brain dry in the air quicker than the other. Goltz concludes from this that an independently acting system of ganglion cells (analogous to the plexus myentericus) is present in the stomach, the irritation of which gives rise to local contractions and peristaltic movements, but which is in connection through the vagi with the medulla oblongata, which exercises a controlling effect on the functions of these ganglia;—an explanation which is quite familiar to us from the reflex controlling centres for the extremities in the spinal cord. If by

destruction of the medulla or section of the vagi the controlling influence is wanting, a very strong action of the centres in the stomach follows stimuli which not only escape the observer, but are without effect on the normal stomach, just as we observe an increased reflex excitability in certain diseases of the spinal cord—for example, sclerosis, hemorrhage, &c. The theory unites proved and unproved views; moreover, the experiment succeeds invariably and without difficulty. But the ganglionic plexus postulated by Goltz, though not proved by him, is present according to Openchowski, who has recently communicated the results of a remarkable series of experiments, extending over years, on the innervation of the stomach. This investigator succeeded in proving the existence of separate complexes of ganglionic cells in the cardia and pylorus, near the structures which are admitted to be extensions of the mesenteric and Auerbach's plexuses. By means of a special method of registration, described on p. 54, and methodical stimulation of special nerves and definite parts of the brain and spinal cord respectively, after section or amputation of particular portions of the central nervous system, this author came to the following conclusions respecting the nervous arrangements which control or regulate the movement of the stomach in its widest meaning.

Opening and closure of the cardia and pylorus, as well as the movements of the intermediate portion of the stomach, are worked automatically by the above-described complex of ganglionic cells. But the stomach is also in relation with certain centres in the brain and spinal cord through the medium of the vagus, the sympathetic, and the splanchnics.

A centre for the contraction of the cardia is situated in the region of the posterior pair of the corpora quadrigemina, and is in connection with the stomach chiefly through the vagi, in a less degree through the spinal nerves, which are derived from the dorsal cord, and take their further course through the vagi. Another centre for the opening of the cardia lies in the cerebral ganglia, where the caudate and lenticular nuclei join near the anterior commissure, and is also connected with the stomach through the vagus (nervus dilatator cardiæ). Independent centres for the dilatation of the cardia seem also to be found in the upper spinal cord, and leave it down to the fifth dorsal vertebra through the boundary zone. In the above-named situations,

however, there are at the same time centres for the movements of the stomach and of the pylorus; contractions of the stomach wall are produced from the corpora quadrigemina, and controlling centres for the same are situated in the upper portion of the spinal cord, whose course lies through the sympathetic and splanchnics. For the pylorus there is a controlling centre in the corpora quadrigemina, while in the olivary body there is another for opening it. There is an express antagonism between the innervation of the cardia and the pylorus, as shown by the fact that stimulation of the nervus dilatator cardiæ makes it act as a closer of the pylorus, and the same may be observed in the higher centres in the cerebral ganglia, and also in the cortical centres found by Openchowski in the crucial sulcus.

We have, therefore, to do with a very complicated mechanism of innervation in the stomach, if these data are confirmed, and the careful and extensive series of researches of Openchowski afford a guarantee of their truth. The contemporaneous opening and shutting of the cardia and pylorus are of great interest. It is a purposeful mutually useful arrangement, similar to that which we shall see later on exists in the innervation of the intestine and also in other places, as, for example, in the self-regulation of the lungs.

Moreover, the experiments accord, so far as concerns the automatic action of the nerve centres in the stomach, with already known facts. Oser saw in stimulation of the vagus contraction of the pylorus, and spontaneous (*i.e.*, regulated by the local ganglia) movements of the pylorus were controlled by stimulation of the splanchnics in the abdominal cavity.

When Hofmeister and Schutz observed the recently excised stomachs of dogs in warm chambers at the temperature of the body, they saw quite typical movements within the first sixty to ninety minutes, the stimulus for which must have been existent in the stomach itself. Certainly it is not yet decided by these experiments whether these were physiological movements of the surviving organ, or whether we have to do with an abnormal stimulus due to the anæmia, a point which the investigators quite overlooked; but the course of the movements appears to have been so typical, that their legitimate character seemed to them undeniable. According to their account, they occurred at first in progressive, gradually increasing waves of

contraction from the cardia to within 2 cm. above the pylorus, in which the muscular wall of the great curvature specially took part. In the place named these contractions came to a stop, and for a short time remained quiet, while at the same time the contraction of the pyloric portion of the stomach began. At a certain moment the organ assumed an hour-glass shape, with a larger cardiac swelling and a smaller pyloric swelling. When the præcentral contraction relaxed, the contraction of the longitudinal and circular fibres of the pyloric portion reached its highest point, contemporaneously without peristalsis, and the entire movement ended with a concluding contraction of the pylorus. In this fashion the contents of the stomach are at a certain time divided into two parts, of which the larger consists, as these investigators consider probable, of the bigger and harder masses, the smaller of the fluid, or at least of reduced material ready for transmission into the intestine. The stomach is one anatomically, but there is no uniformity in its function, as the fundus performs the function of chemical digestion, while the pyloric portion regulates the passage of the chemically-changed contents into the intestine, and possesses a power of selecting the material which is ready for transfer. Gentlemen, I cannot accept this view. The plain fact that the pyloric portion secretes a strongly digesting fluid containing pepsin and hydrochloric acid, proves it to be an important part for the peptonising function of the stomach.

Not in harmony with the above-described movements in the surviving organ are the observations of Rossbach on the living stomach. According to these, the fundus remains without any movement. The contractions begin always at the same place, in the centre of the stomach, run continuously to the pylorus, and remind us only of the descriptions of Hofmeister and Schutz, in so far as the strongest constriction takes place in the region of the antrum pyloricum Willisii.

Openchowski's observations are in harmony with these. In direct opposition to the results of Goltz's experiments is the observation of Rossbach, who found the stomach contracted after section of the spinal cord at the level of the second cervical vertebra or section of the vagi, whereas by analogy with Goltz's experiments it should be dilated. There is a further ground for the belief that in these and Hofmeister's

experiments we have to do with phenomena of irritation from anæmia. According to their view, the pylorus during the whole of digestion must remain shut, and open itself actively at the conclusion so as to allow the stomach contents to escape. I will not dispute the latter relation in dogs; for men, however, it is not valid. The results obtained by Dr. Boas and myself in observations made by removal of the stomach contents with the tube in all stages of digestion, show that chyme passes into the intestine, not suddenly but gradually, and this passage stands in relation to the amount of hydrochloric acid in the chyme, as was proved also by Pfungen in a gastrotomised lad, in whom acids exerted a controlling influence and alkalies a relaxing influence on the pylorus.

But we shall speak of the course of the movements in the stomach and its motor functions, when we come to treat of the passage of the chyme into the intestine (*v.* Lecture VIII.). The other nervous relations of the stomach in connection with its sensibility, and the rightly or wrongly localised general sensations, such as hunger, satiety, &c., and our knowledge of the process of vomiting, will be found described in the second part of this volume, and may be here passed over.

Pure, unmixed *gastric juice* was first known when Bidder and Schmidt produced gastric fistulæ in animals, and at the same time tied all the ducts of the salivary glands to prevent swallowing saliva. Such gastric juice has the following composition:—

Gastric juice of Dog free from saliva. Mean of 10 analyses.		Gastric juice of Man containing saliva.	Blood serum of Man.	
Water	973·06	994·6	903·0	
Solids	26·94	5·4	97·1	
Containing:				
Peptone and pepsin	17·19	3·02	Organ. mat.	88·5
Free hydrochloric acid	3·05	0·22	Inorganic	8·6
Alkaline chlorides	4·26	2·0		7·2
Ammonium chloride	0·47			—
Containing chlorine	**5·06**			**3·6**
Phosphates: Lime	1·73			
Phosphates: Magnesia	0·23	0·15		0·5
Phosphates: Iron	0·08			

Here you have an analysis of human gastric juice as obtained from a gastric fistula, and the comparison with an analysis made by Lehmann of human serum. The large proportion of chlorine in the gastric juice as compared with blood serum will strike you, whilst, conversely, although it is certainly not distinctly brought out by the analysis, there is about one-half less alkali in the gastric juice than in blood. That the human gastric juice in the above table contains about ten times less hydrochloric acid than that of the dog need not astonish you. The first is abundantly mixed with water or saliva, but pure human gastric juice, freed as far as possible from saliva, contains less hydrochloric acid than that of the dog, and varies, according to the analyses of Szabo and Boas and myself, between two and three parts per mille.

The reaction of the gastric juice is always very acid. The mucous membrane of a recently killed animal possesses an acid reaction wherever it comes in contact with the gastric juice. There is little interest in following historically the discussion of the question as to which acids give rise to this reaction. Bidder and Schmidt have proved by an unimpeachable method that it is free hydrochloric acid. They estimated the entire chlorine and the entire bases, reckoning these all as chlorides, in a measured quantity of gastric juice, and found more chlorine than would be necessary to convert the bases into chlorides. This overplus of chlorine can exist only as hydrochloric acid, free or in an organic combination. But the excess of chlorine corresponds to the equivalent of an alkali (barium), which must be added to the same quantity of gastric juice as was used in the experiment up to neutralisation; so it follows that, first, free hydrochloric acid is present; and, second, other acids, if there be any, are present in only very slight traces. This investigation has finally decided the dispute concerning the nature of the gastric acid, which had attained such dimensions that no fewer than twelve authors have pleaded for lactic acid, fourteen for hydrochloric acid, and two for phosphoric acid, finally agreeing with Prout, who as early as 1824 proved the existence of hydrochloric acid in the gastric juice. In such investigations it is necessary to draw a strong distinction between the pure secretion of the gastric mucous membrane and the stomach contents after the introduction of food, which

are a mixture of gastric juice, and according to the nature of the aliment, of very varying matter, salts, &c.

Moreover, there is also present, as already other authors (Lehmann, Frerichs, and others) had suggested, and Dr. Boas and I have proved, an organic acid, lactic acid, in fresh not pathological stomach contents, yet it is not a product of glandular secretion, but is a consequence of the normal fermentation of carbo-hydrates in the stomach, or is brought into the stomach ready made in certain food and only increased there. We find, indeed, in extracts of the gastric mucous membrane slight traces of lactic acid, but these are imbibed from the stomach contents, and are not produced in the membrane, which is shown by the fact that parts destitute of glands, situated at the cardia, also give an acid reaction, and contain traces of lactic acid. We (Ewald and Boas) have shown that at the commencement of the digestion of a meal of bread, or meat with bread or potatoes, by a healthy man lactic acid, or, according to the accidents of fermentation, sarcolactic acid, is always present. It may be demonstrated with certainty during the first ten to thirty minutes after the ingestion of a meal, and then disappears so soon as the quantity of free hydrochloric acid becomes noticeable, till only traces are left. As a rule, there is an intermediate stage between those in which only lactic acid or only hydrochloric acid is present, in which both may be met with. In fasting, unstimulated stomachs there is neither lactic acid nor hydrochloric acid, but after a meal not containing any lactic acid-producing matter, such as pure egg albumen, the stomach contents can be shown for any length of time to contain only free hydrochloric acid, and this is the case almost immediately, or from seven to ten minutes after eating. It appears to begin at the moment of the introduction of food into the stomach, but is taken up so long, and is, therefore, not present in a free state, as it on the one hand meets with albuminous bodies, which imbibe it and form with it close combinations, and on the other there are salts or bases whose affinities must be satisfied. So long, therefore, as there is room for all kinds of fermentative processes, *it is not possible to fix the time at which free hydrochloric acid is present in the stomach*, and all estimates, of which a number exist in literature, are valid only for the kind of meal used in the case in question.

There is, however, as we (Ewald and Boas) have stated in our work published in 1885, *a certain antagonism between hydrochloric acid and lactic acid*, so that in proportion as the former increases in amount and is found free in the stomach, the formation of the latter is arrested, and that by the absorption and transference of the stomach contents into the intestine it gradually disappears. This view is indeed disputed by Rosenheim, who thinks "there can be no question of such an antagonism," but it has been confirmed by E. Cohn in a series of experiments performed under the direction of Hoppe-Seyler. According to these, acetic acid fermentation is inhibited by traces of free hydrochloric acid, 0·05 parts per mille. Lactic acid fermentation, indeed, requires more to prevent it, namely, 0·7 per mille, but this figure is a good deal below that of the normal gastric juice, which contains 2 to 3 per mille. It is understood that we are speaking of free acid, or the combination of chlorine, pepsin, and hydrogen, for the inhibition does not take place so long as albumen, or bases or salts are present in the stomach and combine with the acid secreted. But it cannot be sufficiently emphasised that in the discussion of the above questions and cognate subjects in the range of pathology, we must distinguish between the hydrochloric acid actually secreted and that demonstrable as free acid in the stomach after the introduction of food. From not considering this circumstance, a number of contradictory statements exist, and to this may be traced the controversy between Rosenheim and Ewald and Boas (*v.* Centrlbl. f. d. med. Wissensch., 1889, p. 242, et seq.). Our statements, which were contested by Rosenheim, but, let it be said at once, were confirmed by numerous authors, referred to the demonstration of free hydrochloric acid in the stomach and the actual time of its appearance after a fixed meal, whilst Rosenheim referred to the presence of the actually secreted hydrochloric acid which in certain early stages of digestion is combined with the albuminates, salts, and bases of the ingesta. It is plain to any moderately educated chemist, though, as we have observed, it was for long overlooked, that free acids can only exist in a complex fluid when all its basic components are satisfied.

Moreover, when we consider the methods of demonstrating acids in the stomach contents, we must distinguish between testing

for free acids and testing for acids actually secreted or formed by fermentation.

For the practitioner, it is of the first importance to discover free acid in the stomach contents and to determine its nature. As I shall discuss this subject in the second part of this book, I need say here only briefly that the best reagent for free hydrochloric acid is that recommended by Günzburg, composed of phloroglucine 2 grms., vanilline 1 grm., and absolute alcohol 30 grms. The reaction is that a splinter dipped in the solution becomes deep red when touched with hydrochloric acid, due, according to Singer, to the presence of vanilline. Fluids which contain one-twentieth part per thousand of free hydrochloric acid, give with this reagent, if previously warmed, crimson streaks varying in intensity with the amount of free acid present. If we have to do with a solution of unknown strength, it is possible to make an approximate estimation by repeated dilutions until the reaction scarcely appears.

The precautions necessary to take with this reaction, and the other tests for free acids or acid salts, as well as the estimation of the acidity of the stomach contents, will be found in the second part of this work. In the stomach, however, hydrochloric acid can exist not only in a free state, but also combined with bases and bodies comporting themselves as bases (albuminous bodies and their derivatives), but these give a negative result to the reaction for free acids. Would we know, moreover, whether the acid is actually secreted, we must employ a procedure by which the acid, or rather the essential part of it, the chlorine, is driven out of combination and estimated as such. Of all the methods hitherto proposed, that of Sjöqvist is the best. It consists in neutralising a definite quantity (10 cc.) of filtered stomach contents with barium carbonate and then reducing it to ash. By this means all the organic compounds of hydrochloric acid are converted into barium chloride, and this may be estimated by means of a solution of bichromate of potash. We have often employed this method, and have proved its utility and accuracy, provided that the greatest care is taken to avoid all chlorine-containing reagents, filter papers, &c.

For lactic acid we possess a very good and certain test, provided we avoid fallacies from impure reagents, in a weak

solution of ferric chloride or a mixture of a few drops of carbolic acid and ferric chloride diluted with water to the colour of amethyst blue. The amethyst blue or quite pale yellow colour turns in the presence of very minute traces of lactic acid (less than half per mille) to a bright canary yellow. It can be used directly to the filtered stomach contents, as it is not affected by the presence of peptone or of salts; but if there is any reason to doubt its accuracy, or should the colour not be a beautiful yellow (and this only is characteristic), a small quantity of the stomach contents should be shaken with ether, the ether evaporated, the residue taken up with a little water, and the reaction repeated with this, the result then being absolutely certain.

The ferric-chloride carbolic solution serves also, as may be interpolated here, for the recognition of the fatty acids occasionally present, especially butyric acid, which gives the amethyst blue solution a smoky yellow colour. If we perform the somewhat troublesome extraction with ether, the result of the reaction is confirmed by finding fat drops in the ethereal residue when taken up with water, for there is always fat in the stomach contents when fatty acids are present, and this is dissolved by ether.

With the aid of these reactions we can recognise the nature of the acids in the stomach contents within certain limits.

The procedure of Richet-Berthelot, formerly described and confirmed by me, for estimating the so-called co-efficient of partage, depends upon the different but constant capacity of ether to take up mineral and organic acids.

If an acid fluid is shaken with ether, the latter assumes a different, but for each acid a constant degree of acidity, which is easily estimated; it is possible to estimate such acid present in a mixture of unknown organic and inorganic acids by successive shakings. This method is practicable for simple pure chemical mixtures of acids, but it is not only very troublesome, but it is not possible to employ it, as I have shown, in the conditions of the gastric juice. It has led Richet to the false conclusion that the hydrochloric acid is secreted in combination with leucin. Apart from the fact that I have directly proved that leucin (and tyrosin) are not present in the secreted gastric juice or in the mucous membrane of a fasting animal, the

method of successive agitations with ether cannot be employed, and is not practicable in a mixture of organic bodies—acids and bases—alone, or in combination with inorganic acids, as is always the case with the gastric juice.

Leucin and tyrosin are present, as was shown by Kühne and Uffelmann, long before Richet or even myself, in the gastric contents and stomach mucus of a digesting animal, but they are to be regarded as the products of decomposition of the ingesta and not as the products of glandular secretion.

The proportion of hydrochloric acid in pure human gastric juice, in accordance with statements already made for the dog, is given by Szabo as three per mille, whilst Richet found 1·3—1·7 as the mean of seventy observations. His investigations were made upon a gastrotomised patient with an impermeable stricture of the œsophagus.

Now-a-days we do not find it necessary, like Gosse, who swallowed air in order to vomit his stomach contents, to give emetics in order to obtain the stomach contents at any time. Since we have taken to use the soft india-rubber tube instead of the old stiff pipe, the introduction of the "stomach-tube" has become greatly facilitated.

It is not difficult to obtain so-called undiluted gastric contents, that is, chyme formed after a given meal, without the use of a stomach pump or siphon. It is only necessary to introduce the tube and press on the abdomen to obtain gastric juice relatively little diluted.

The numerous observations I have made on people two hours after swallowing some green tea (without milk or sugar) and dry white bread, have shown that the proportion of hydrochloric acid lies between 1·5 and 2 per mille, and consequently for pure gastric juice must be somewhat higher.

That the hydrochloric acid is formed from the chlorides of the blood is *a priori* to be concluded, and has been experimentally proved by the investigations of Voit, and especially through the careful series of experiments of Cahn, which showed that the hydrochloric acid disappeared when chlorides were excluded from the food.

The hydrochloric acid is formed by the splitting up of the various chlorine compounds, especially chloride of sodium, the alkali remaining in the blood.

During digestion, that is, when hydrochloric acid is secreted in the stomach, the blood becomes richer in alkalies than it is during the repose of the stomach glands, and at the same time the urine secreted is richer in alkalies, less acid, and even sometimes distinctly alkaline. Bence Jones actually made these observations, and taught this quite correctly in the beginning of this century (1819). By other investigators, Quincke, Maly, Görges, Hübner, and Sticker, they have been confirmed and extended, so as to embrace pathological conditions. It is obvious that the relations between the ingestion of food and the urine must fail when the diseased stomach secretes no hydrochloric acid, and it may be stated that the deficiency of acid in the urine gives some idea of the amount of hydrochloric acid secreted—of course only provided that the increased alkalinity of the urine is not due to the absorption of alkaline food, as is suggested by Roberts.

But if the latter were the case, the deficient acidity of the urine would not fail to appear, in spite of deficient production of hydrochloric acid in the stomach, in cases of cancer or atrophy of the stomach, or in severe gastric catarrh, so long only as the absorbing power of the mucous membrane was preserved, and on the other hand it could not occur if the secretion of hydrochloric acid was excited by ingesta very poor in alkali.

Finally, the ordinary diminution of acidity must take place if absorption is delayed, but the formation of hydrochloric acid not interfered with. The experiments which Hübner and Sticker have made under the above-named conditions support the theory of Jones and the law formulated by Quincke, that diminution of the acidity or alkalinity of the urine may be effected in two ways: first, by the taking up of large quantities of alkali in the blood (alkalies combined with carbonic acid or vegetable acids, absorption of alkaline exudations); and second, by loss of acid to the organism, by vomiting the acid contents of the stomach, or by the combination of the bases to form insoluble salts. The latter was pointed out by Maly, who administered calcium or magnesium carbonate to dogs, in which he had excited a strong flow of gastric juice, and found that after fifteen to twenty minutes their previously acid urine became alkaline. The excretion of hydrochloric acid causes a physiological want of acid in the organism resembling the want of alkali which results from

the secretion of the alkaline pancreatic juice. At this time, however, the urine must undergo a change, as Quincke declared, in the direction of increase of acidity. Both processes balance each other, and to some extent occur side by side, and control each other to a certain degree. This accounts for the variations in the acidity of the urine in the course of twenty-four hours, which, however, do not always strictly conform to these conditions. The hydrochloric acid secreted during digestion is absorbed in the form of chlorides or loose combinations with peptone, and compounds of chlorine from the food are taken up, so that we find (Sticker) the excretion of chlorides in the urine increased after the principal meal, but also at times reduced by the action of salts, such as calcium carbonate, which form little soluble chlorides, hindering the absorption of hydrochloric acid.

There still arises the interesting and hitherto puzzling question, what are the causes that bring about the secretion of acid, and, moreover, of a mineral acid gastric juice from the alkaline blood? A brilliant experiment of Maly's has thrown an unexpected light upon this. There are fluids of alkaline reaction containing an acid and an alkaline salt which are mutually inactive, but still give an alkaline reaction, because the acid reaction is to a certain extent eclipsed: for instance, a solution of neutral phosphate of soda ($Na_2\ H\ PO_4$) and acid phosphate of soda ($Na\ H_2\ PO_4$) is alkaline. Such a solution placed in a dialyser after a short time gives up its acid salt to the surrounding distilled water, and one has in the dialyser an alkaline fluid outside an acid fluid. Maly proved that in blood, in spite of its alkaline reaction, acid phosphate of soda as well as free hippuric and uric acids are present. These acids and acid compounds have a greater diffusive power than the neutral salts. Hence the excretion of acid urine from the renal parenchyma is analogous to the action of a dialyser. Further, if we mix together neutral phosphate of soda with calcium chloride ($Ca\ Cl_2$), we get calcium triphosphate, sodium chloride and free hydrochloric acid, as in the following equation:—

$$2\ Na_2\ HPO_4 + 3\ Ca\ Cl_2 = Ca_3\ PO_4 + 4\ Na\ Cl + 2\ HCl.$$

According to the harmonising statements of Pribram and Gerlach, lime ($Ca\ O$) is present in the blood, and therefore allows

an opportunity for the formation of free hydrochloric acid. Hydrochloric acid possesses a high diffusive power—it passes thirty-four times (Graham) as quickly through the dialyser as common salt; and this explains how, once formed as above in the blood, it may pass into the gastric juice in such large quantities as in fact we find it to do. The facts that we secrete acid urine and acid gastric juice are meanwhile divested of their strange characters by the aid of this simple process of diffusion; but the question why phosphatic salts are only diffused in the kidney, and hydrochloric acid in the stomach, and that indeed only periodically, must be left for the future to answer, as the hypothesis of Maly in support of his theory, that the peptic glands and also the kidneys and sweat glands constitute diffusion bodies, is still only a description of existing relations unsupported by any facts.

These ideas have been also expressed by Heidenhain, but he has not named perhaps the most important difficulty, that of physically explaining the *periodical* secretion of hydrochloric acid, although in all other glands which secrete periodically, that is, through a special nerve stimulus, a specific secretion, we conclude that this is formed by the specific activity of the secreting cells, whilst the common source, the constituents of the blood serum, exhibit a very changing composition. Heidenhain asserts, on the faith of a discovery of Grützner, according to which the amount of chlorides in the gastric mucous membrane is proportional to the amount of peptone, that the hydrochloric acid is separated from the chloride of sodium in the glands, by the aid of organic acids and even of lactic acid. Landwehr says the same, and derives the necessary lactic acid from a ferment formed in the stomach mucus. But this hypothesis fails in the chief point, that is, the necessary lactic acid, as Leube and Boas and I have shown that on feeding with pure albumen there is a strong hydrochloric acid reaction in the stomach, but not a trace of lactic acid is to be found. Ellenberger and Hofmeister, too, have directly shown that in the stomach of the horse, which is specially suitable for such experiments, hydrochloric acid is only found in a limited part of the stomach, in the fundus portion, where parietal cells are present, while lactic acid and chlorides may be found everywhere.

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LECTURE VI.

Gentlemen,—As you know, there is in the gastric juice and glands a ferment, pepsin, the action of which on albuminous matter will occupy us more fully. I omit to enter into the methods that aim at its pure production, because none has yet completely attained its object. We obtain a ferment mixed with other matter when a glycerine extract of gastric mucous membrane is treated with alcohol in excess. A white precipitate falls, which on drying forms a white powder. This is soluble in water, and has the characteristic pepsin action. It can be heated to 100° without losing this. The preparations in common use, German and French pepsin, pepsin-ptyalin, &c., are only mixtures containing more or less pepsin or ferment, albuminoids and starch. I have for some years made analyses of the current preparations, tested their action, and published the results; therefore I will not return to the subject, as in the meanwhile the articles have been greatly modified. Such analyses must be repeated from time to time if we wish to estimate the value of the commercial preparations. As to what we should expect, I may give the statement of Petit, that active pepsin should peptonise one thousand times its own weight of fibrine, and in seven hours five hundred thousand times its weight. The best method to prepare a strong peptonising fluid is by extracting the gastric mucous membrane, by which means no doubt we obtain not only pepsin, but also albuminous bodies and salts. We can obtain a pepsin extract mixed with many other substances by carefully washing the minced mucous membrane dissected off the muscular coat, of a fresh pig's stomach, either by the old method given by Eberle in 1834, by infusion with a three per mille solution of hydrochloric acid, or, according to v. Wittich, with glycerine, or, after Erlenmeyer, with a saturated solution of salicylic acid or formic acid solution (1 : 1000 sp. gr. 1·205). All are very practicable; the best, according to my experience, being the two first named. The glycerine infusion has the advantage of the

greatest strength and most easy preparation. If we want to eliminate impure matter as much as possible, the mucous membrane must be treated previously with strong alcohol, which does not touch the pepsin, but precipitates a part of the albumen and lixiviates the salts. I allow 500 ccm. of glycerine to a pig's stomach. It remains in this a day until the glycerine extract is active. Then it must be filtered through a fine cloth, and we obtain an extract almost as clear as water, of which very small quantities, a few cubic centimetres, act very energetically.

C. Sundberg has obtained a very pure pepsin in the following way: the mucous membrane of the stomach is extracted with concentrated salt solution, the salt dialysed away into an acid solution, the separated flocculi of albumen filtered off, and the filtrate allowed to stand eight to fourteen days for self-digestion, in order to destroy the rennet ferment, and to convert the albumen present into peptone. The solution is then precipitated with calcium chloride and sodium phosphate, in order to precipitate the pepsin. The precipitate is washed, dissolved in as little as possible of 5 per cent. hydrochloric acid, and the salts removed by dialysis. The remainder consists of nearly pure pepsin solution, which digests energetically, contains no albuminous bodies reacting to the ordinary tests, and is only precipitated by alcohol (pepsin). Kühne and Chittenden found that ammonium sulphate precipitates not only all non-peptonised albumens but also pepsin from hydrochloric acid solutions, and that the pepsin may be redissolved in dilute acid, and is relatively pure and fit for further digestive experiments.

If we wish to carry out these experiments we must remember what, *mutatis mutandis*, we have already noted in the salivary glands, and we shall have occasion to observe in the pancreas, that the gland cells do not form the specific ferment, pepsin, but a previous stage of it, a pepsinogenous substance, pepsinogen (propepsin, Schiff), which during the process of secretion becomes pepsin, so that, as Ebstein and Grützner have found, the extract of the gland cells is inactive upon albumen without the addition of hydrochloric acid, but may be converted into pepsin by treatment with sodium chloride or hydrochloric acid, and, as Langley shows, the pepsin is destroyed by sodium carbonate, while the pepsinogen is scarcely affected by it. If we extract a

gastric mucous membrane with glycerine the pepsin is taken up, but no pepsinogen, while watery non-acidulated infusions of the membrane contain pepsin and pepsinogen.

The specific action of gastric juice, or of what is the same for this purpose, the pepsin or pepsin extract in acid solution, asserts itself by a definite action on albuminoids, which are converted into a modified form, the so-called peptone of Lehmann. The tangible, practical object, if I may so express myself, of this change is to form out of a little diffusible body (albumen) one easily diffusible (peptone), which is capable of absorption through animal membrane in a higher degree than ordinary albumen. In fact, Funke has proved that the endosmotic equivalent of albumen is over 100, and that of peptone 7·1—9·9, that is, about 12 times more of the latter than of the former would pass through the septum; and Acker saw that peptone solution may be forced under a certain pressure more easily through an animal membrane than ordinary solution of albumen. But this only holds good for acid solutions of peptone, and is reversed for a mixture of peptones and salts (Maly, Henninger), so that other physical differences unknown to us must exist between albuminates and peptones which occasion the undoubtedly greater capacity of the latter for absorption, supposing that the selective power of the epithelium of the mucous membrane is a physical process and not vital. The peptonisation of albuminous bodies may be brought about in the following way: if ordinary egg albumen, or well-washed fibrine is put into a dilute acid solution, it rapidly swells up and forms, if only a little acid has been used, a compact jelly-like mass. A part of the albumen becomes dissolved as the so-called acid albumen, syntonin (Meissner's parapeptone), which is a combination of albumen with the acid, and may be precipitated from the acid solution by weak soda solution in the form of a white precipitate, and is called the precipitate of neutralisation. In so far as this body is not changed by the peptonising process about to be described it is called by Kühne anti-albuminate. But if we add some pepsin or pepsin containing extract to a mixture of albumen and solution of hydrochloric acid (2—5 per mille), and keep the mixture at the body temperature, the albumen, fibrine, &c., dissolve rapidly, the fluid becomes clear, and we find at the bottom of the glass a varying quantity of undissolved albumen, according to the

proportions of albumen, pepsin, and acid present. If this is now filtered off we get a solution which contains, besides the above described syntonin, whose amount varies with the duration of the digestion, but finally disappears only very late, peptone and the various intermediate products between native albumen on the one hand and peptone on the other. The latter, which are collectively described as albumoses, are a transition stage between albumen and peptone. Their presence and amount depend upon the duration and intensity of the fermentative action. They form a series of albuminous bodies, for the knowledge of which we are indebted chiefly to W. Kühne. Kühne divides them into protalbumose, hetero-albumose (dysalbumose), deutero-albumose, antialbumide, and antideutero-albumose, of which we may only state here that they are distinguished chiefly by their behaviour with sodium chloride and saturated solution of ammonium sulphate, their solubility in acidulated water, and their coagulability by heat. But these bodies also differ by in part becoming peptones, which by the action of the pancreas are further split up, and in part resisting the action of the pancreas, so that we shall give their features in discussing the pancreatic digestion, and we may abstain from stating all their reactions, as it is still an open physiological question how far they are actually chemically distinct bodies, how far their differences are occasioned by the varying relations between acids, alkalies, and albumoses (Herth).

But I must condemn the classification based on their superficial affinities which F. Röhmann (Anleitung zum chemischen Arbeiten, Berlin, 1890) has given. The most important of these bodies is the body called by Kühne protalbumose, by Schmidt-Mulheim propeptone, which is precipitated from its acetic acid solution by concentrated brine or rock salt solution, which becomes cloudy on slight heating, but on further heating again becomes clear, so that it remains clear at temperatures which coagulate native albumen, but on cooling reappears. Salkowski has prepared it in a pure form and has described it as just given. However, it is doubtful whether propeptone is necessarily formed as an intermediate product in the gastric digestion of albumen. According to the researches which Dr. Boas carried out in my laboratory, it was constantly absent with purely meat food, but appeared under certain circumstances with pure egg albumen,

and was always observed in the digestion of fibrine. Neumeister objects to these experiments, on the ground that the method employed by Boas based on the above-stated properties of propeptone (precipitation in the cold by the addition of concentrated brine and acetic acid, disappearance of the precipitate on heating) is not sufficient, because certain albumoses nearly allied to propeptone (protalbumose), such as Kühne's deutero-albumose, are not excluded by it. A negative result of the above test cannot prove the absence of these bodies, which can only be distinguished by the addition of ammonium sulphate or rock salt to saturation.

I will not dispute this, indeed from a repetition of Boas' experiments I can say, that when the test with brine and acetic acid fails, a precipitate may be obtained with ammonium sulphate. But the experiments of Boas were not concerned to prove that all albumoses were absent, but that the reaction which gives positive results with a certain group, the propeptones, remains negative with the others; that in the one case the conversion of albumen into peptone is accompanied by the formation of propeptones (protalbumoses), in the others it is not.

If the above described mixture, that is, a compound of albumen, pepsin and a solution of hydrochloric acid of 2—3 parts per mille, kept at the body temperature till the albumen is completely dissolved, or the stomach contents after ingestion of an albuminous meal, be precipitated with ammonium sulphate, all the albumoses formed during digestion and not already converted into peptone are thrown down, and we have in the filtrate a fluid which gives all the characteristic reactions of pure peptone. 1. It does not coagulate on heating. 2. No precipitate occurs on saturation with sodium chloride and the addition of concentrated acetic acid, either with heat or in the cold. 3. It gives a purple violet colour with copper sulphate in alkaline solution, which, contrary to many statements, is distinguished very sharply from the pure violet colour of ordinary soluble albumen when treated in the same manner. The latter becomes purple on heating only, peptone gives the colour in the cold. This reaction, the so-called biuret-reaction, must be carefully conducted with regard to the proper proportion of sulphate of copper to the peptone present. If there is too little copper the reaction is only seen when the first drops are added. If too much copper

is added, and there is only a little peptone present, the reaction is masked by the blue colour of the copper. It is noteworthy that the biuret-reaction is obtained with propeptone as well as peptone. 4. The xanthoprotein reaction and the reaction of Millon give a positive result. 5. With glacial acetic acid and concentrated sulphuric acid the fluid becomes violet-coloured and faintly fluorescent, and in a certain concentration gives a band in the spectrum like that of hydrobilirubin between the green and the blue. These colour reactions, given under 4 and 5, are peculiar not only to peptone but to all albuminous bodies. 6. No precipitate is caused by addition of the following reagents, which throw down albumen and albumoses: nitric acid, acetic acid, acetic acid and ferro-cyanide of potassium, acetate of lead and ammonia, metaphosphoric acid, ammonium sulphate, salts of the heavy metals. 7. Precipitation occurs with mercuric chloride in neutral solution, hydrochloric acid and metaphosphoric acid, phosphomolybdic acid, tannic acid in weak solution of acetic acid, absolute alcohol (Neumeister).

If it is desired to obtain the peptone in substance from this solution it can be done, as Kühne directs, by treatment with ammonium sulphate evaporation and crystallisation, treatment with absolute alcohol, boiling with hot saturated carbonate of baryta solution to drive off the ammonia, precipitation of the barium compound of peptone by alcohol and decomposition of the baryta-peptone by sulphuric acid, when we obtain a hygroscopic powder difficult to preserve in a dry state (Kühne's ampho-peptone), which possesses a nauseous bitter taste, and the peculiar property when moistened with a drop of water of effervescing and evaporating like phosphoric anhydride. The above-described filtrate of the digestive fluid after the precipitation of the albumoses, contains, so soon as the digestion has lasted not too short a time, still further modifications of albumen which are regarded by some authors as the products of pepsin action, but by Kühne as impurities due to the mode of preparation of the pepsin extract from the stomach. These are leucin, tyrosin, and other bodies to be afterwards described, which after removal of the peptone as described, or after its precipitation with alcohol, remain in the residue. Neumeister has shown that a pure solution of pepsin does not give a violet colour with chlorine water, showing the absence of leucin and tyrosin.

The process of peptonisation may be represented in the following table, in which the thick brackets denote the precipitate:—

Albumen (*i.e.*, fibrin, serum albumen, egg albumen, muscle albumen, casein, vegetable albumen, &c.)

+

Gastric juice (pepsin or glycerine, &c., extract of mucous membrane + solution of hydrochloric acid of 2—3 per mille)

is kept at 37·5° and digested. The solution becomes eventually, after separation of the unchanged albumen by boiling with acetate of soda and acetic acid and filtering, neutralising with soda and filtering again:—

Syntonin

Albumoses (proto- and deutero-albumoses [propeptone], hetero- and dysalbumoses, antialbumide).

Treated with concentrated ammonium sulphate solution, or saturated with powdered ammonium sulphate, or rock salt, and brine-saturated acetic acid added drop by drop:—

Albumoses

Treated with absolute alcohol, or after Kühne's above-described method:

Peptone (amphopeptone)

Leucin, Tyrosin, &c.

For the pure preparation of peptone it is naturally of the greatest importance that the materials used should be as far as possible chemically pure. This is not the case in our ordinary digestion experiments, and is only under special provisions possible, of which in the above description, which only gives the general outline of the chemical relations, no mention is made.

Pure peptone is so difficult to prepare that the various workers who have investigated this body have described quite different

bodies as pure peptone, and have given correspondingly diverse definitions of it.

It can have no interest for us to recall the history of these well-worn investigations. Recently Maly, Henninger and Herth, Kossel, and especially Kühne with his pupils Chittenden and Neumeister, have claimed to have actually prepared pure peptone. However, the first three authors have not obtained pure peptone, but only albumoses. This is shown not only by the large amount of carbon which their analyses give, namely, 51·58 per cent. (Henninger) and 51·40 per cent. (Maly) against the carbon in fibrin, 52·51 per cent., but also from the statement of Maly, that his solution of peptone in acetic acid solution becomes cloudy, or is precipitated on the addition of yellow prussiate of potash, whilst it is now universally recognised that a digestive product is peptone only when the reactions of albumen and albumose no longer occur. In fact, the figures which Kühne and Chittenden have obtained as a mean of five analyses for hemi-albumose without ash formed from fibrin—

$$C = 51{\cdot}14$$
$$H = 6{\cdot}67$$
$$N = 16{\cdot}86$$

closely resemble those found by Maly and Henninger in their so-called peptone; whilst Kossel for fibrin peptones and Kühne and Chittenden for the so-called amphopeptone (see later under pancreatic digestion), a product of prolonged pepsin digestion, found the following as a mean of ten analyses:—

Kossel.	Kühne and Chittenden.
C = 48·97	C = 48·47
H = 7·06	H = 7·02
N = 15·14	N = 16·86
S = 1·16	S = 0·77

These analyses give a much smaller amount of carbon than is present in fibrin (C = 52·51, H = 6·98, N = 17·34), and was present in the substances described as peptone.

According as peptone is formed from casein, fibrin, or serum albumen, slight differences are to be observed in its relation to polarised light, which all peptone solutions rotate to the left. The body prepared by Henninger was white, amorphous, easily pulverised, destitute of smell and taste, dried at 118°, and at 160° to 180° was decomposed into water and foul-smelling

gases. It dissolved in water and acetic acid, and gave the above-named reactions. The peptone prepared by Kühne was a loose yellow powder, which assumed a constant weight at 105°, and possessed the above-described properties.

What, then, are these peptones? What position do they occupy among the albumens?

Adamkiewicz has endeavoured to maintain, on the basis of a very able investigation, that chemically they are nothing but albuminates, which differ from the ordinary albumens by containing rather fewer salts, and by their somewhat different molecular composition. But he, like his predecessors, only had propeptones before him, so that his opinions and conclusions fall to the ground.

To a similar conclusion, based apparently upon the investigation of a purer material, comes A. Poehl. According to him, peptone, by treatment with alcohol or alcohol-ether, gives some of the characteristic reactions of albumen prepared from fibrin and no changes of rotatory power or of refraction. As an important alteration in the atoms of the molecule without influencing its optical relations is inconceivable, Poehl believes that we must discard the idea of a chemical change in albumen as a consequence of peptonisation, and he accepts the "swelling theory," according to which the change of albumen into peptone is conditioned simply by different degrees of solubility and capacity for swelling. Admitting that Poehl really worked with pure peptone, which, so far as my information goes respecting this Dorpat thesis, is not certain, the entire "swelling theory" is encumbered by many improbabilities, and it is not thoroughly established that the changes of molecular structure are always accompanied by changes in optical relations, or that, on the other hand, bodies with equal rotatory power must have always the same arrangement of the atoms in the molecule. Thus, grape sugar, freed from water, rotates, according to Tollens, +53°1, that containing water only +48°27, and yet Niemand holds that the arrangement of the atoms in the molecule in both cases is not identical.

Most workers, especially Hoppe-Seyler and Danilewski, as well as Neumeister, take the view that first albumose and then peptone are formed from ordinary albumen by the addition of water, and that these bodies arise in the same way as, for example,

grape sugar from starch, with the difference which the albumens derive from the digestion, that the hydration proceeds from the splitting up of the albumen. Henninger has proved this directly by comparing the composition of his peptone with the original albumen; and, in fact, he has performed the experimentum crucis, by reconverting his peptone by dehydration (boiling with acetic acid anhydride at 80°) into a body which had all the properties of syntonin, that is, of the next modification of albumen. Hofmeister attained the same end by heating fibrin peptone to 140°—170°, and Krukenberg and Neumeister converted fibrin and albumen into albumoses and peptones by the action of high-pressure steam. So that here we have an illustration of the description given in the first lecture of the action of ferments, namely, that of constituting a sort of Bunsen's flame in the organism. In fact, there can now be no doubt that peptones (not only by analogy, as Bunge wrongly believes, but proved by experiment) are to be considered the hydrates of the albuminates.

This follows from the facts which may be here recapitulated: 1. Peptones contain less carbon and nitrogen than albumens. 2. They are reconverted into albumen by dehydrating substances. 3. The conversion of albumen into peptone is accompanied, as Danilewski has shown, by an increase of weight, which is only possible by the addition of water. Finally, it may be stated that B. Danilewski found the specific heat of (pure ?) peptone to be 5334, 4876, and 4997 calorics for 1 of material, that is, less than that of the albumens.

You see, gentlemen, that peptone, in course of time, has got on badly. After having disputed for so long what peptone was or was not, they have not only taken from it its greater diffusibility, which was so important for the question of absorption and for the object of peptonisation, but they now deny that there is any important structural alteration in it as opposed to native albumen. Indeed, it remains doubtful, as we shall see later on (Lecture XI.), whether, in fact, peptone or its earlier stages, the albumoses, is absorbed.

During digestion the gastric mucous membrane is more or less saturated with peptone, and, according to Hofmeister, appears to be modified thereby in a peculiar way. If we divide in two nearly equal parts the stomach of a recently killed digesting dog, and examine the first at once and the second after a lapse of

time, about two hours, we find in the last much less peptone than in the first, so that Hofmeister believes that this loss is brought about by a vital action of the surviving mucous membrane, but it is not known what has become of the peptone which has disappeared, or what has happened to it.

If peptone is injected into the blood in large quantities it causes a toxic depressing effect on the central nervous system, and after some sleepiness and somnolence may lead to the death of the animal. This, perhaps, explains the sleepiness that occurs after heavy meals, that is, after the introduction of a large quantity of peptone into the blood; but we shall return to this, as well as to the subject of the channels by which peptone leaves the stomach or intestine, in the chapter on absorption.

Another remarkable property of peptone is, that when introduced in small quantities into the circulation it destroys or delays the coagulability of the blood by dissolving the white blood corpuscles, and lowers the blood pressure so as to kill the animal. However, this property is not peculiar to it, as Kühne-Pollitzer and Neumeister have obtained the same result with the different albumoses, and, according to the experiments of Professor Salvioli, of Genoa, the diastatic ferments exert the same influence. An extract may be made from leeches, as Haycraft has shown, which, when injected into the living blood, or added to that obtained by venesection, delays coagulation for a long while. In all these instances we have to do with the toxic action of a ferment, which, by the destruction of numerous leucocytes, makes the blood more or less incapable of coagulating, so that the action of peptone must be regarded as only an illustration of a general process.

Finally, we must refer to the bitter taste of all peptone solutions, because the intensely bitter taste of vomited matter, which we always used to attribute to the bile mixed with it, is in all probability, as O. Liebreich first suggested, caused by peptone.

Besides its peptonising property, gastric juice, as you know, also possesses that of effecting the curdling of milk. In the preparation of whey, this has the most extensive employment, as the so-called rennet is nothing but gastric juice, or rather gastric juice imbibed by the gastric mucous membrane. Hammarsten has succeeded in isolating from gastric juice a body differing from pepsin, which affects the coagulation of milk in neutral or acid solutions without changing the reaction. He

describes it as the rennet ferment. According to the suggestion of Langley, and the more recent researches of Klemperer and Boas, there is also an early stage of this ferment, a proenzyme or rennet zymogen, out of which is suddenly formed the specific rennet ferment, just as pepsin is formed from pepsinogen. But the rennet ferment may be extracted from the gastric mucous membrane by the action of hydrochloric acid; and quite in opposition to one's expectations, in the newly-born, for whom it is so much needed, it is found to be present, but by no means in greater quantities than elsewhere. Its presence in the gastric juice is demonstrated by the coagulation of milk, and its separation into curd and whey when equal parts of neutrally reacting and filtered milk and carefully neutralised gastric juice are kept at the temperature of the body for from ten to fifteen minutes. The ferment is killed by the addition of alkaline carbonates. If the reaction is acid, peptic digestion takes the place of the curdling process. If the stomach contents contain only rennet zymogen, and coagulation does not occur with the above-described treatment, the zymogen may be converted into ferment by the addition of dilute hydrochloric acid or a five per cent. solution of calcium chloride. At the commencement of digestion, and during fasting, only the proenzyme is present in the glands or in their secretion, which obviously becomes converted into the ferment as secretion of acid increases. But in milk there is milk sugar, which by treatment with gastric juice is partly converted into lactic acid, and remains unchanged when treated with Hammarsten's rennet ferment; so we have nothing to oppose to the further conclusion of Hammarsten, that besides the "rennet ferment" there also exists in the gastric juice a "lactic acid ferment," especially as Ellenberger and Hofmeister state that they have been able to extract from the stomach of the horse both rennet ferment and the lactic acid ferment. There still remains the question whether, in this case, they had to do with a pre-existing ferment, or with the action of an accidentally present lactic-acid-forming micro-organism. I have made some experiments with Dr. Boas by introducing starch solution or sugar (maltose) into the clean, well-washed stomach of a healthy man, and no lactic acid was formed. Dr. Rosenheim has contested this result, but recent experiments have confirmed our statement that in many cases no formation of lactic acid takes

place, and that where it occurs pathological conditions are present, though not such as need give rise to any subjective symptoms of ill-health in the individual concerned.

The action of the gastric juice or acid pepsin solutions should be, according to the theory of ferments, quite endless—that is, they should be able to convert any quantity of albumen into peptone. But this is not the case. In an artificial digestive mixture, the process comes to an end after a certain time, before all the albumen is digested, by the accumulation of the products of fermentative action, as already explained. We must then add more acid, or dialyse away these products. In what manner the acid is utilised has not been hitherto satisfactorily explained. According to Hoppe-Seyler, it forms acid compounds with the albuminoids present (syntonin and peptone). At length the addition of acid no longer helps in the digestion of further quantities of albumen; the pepsin becomes inactive, probably decomposed. The necessary quantity of pepsin, compared to the quantity of albumen finally digested, is always surprisingly small, and this circumstance supports the belief that pepsin is a true ferment, in spite of the theoretical claims being, as we saw, incompletely satisfied. This is the place to say a few words respecting the much-discussed "loading" theory of Schiff, which, though not tenable in its original shape, has obtained some support from experiments of Herzen, which should not be too lightly appreciated. Schiff believed that the formation or secretion of pepsin depended upon the introduction into the stomach of certain "peptogens"; for example, meat, bread, bone, dextrine, &c., and the glands were to some extent first "loaded," according to the claims made by the food taken. The grounds on which the Genevese physiologist rested cannot stand stringent criticism, and the differences in the amount of pepsin present in the various stages of digestion which Schiff found may well have been due to the greater or less amount of propepsin converted into pepsin. But as a matter of fact, the food present is not without its influence on the rapidity of the digestion of albumen, as was shown by Herzen in a most demonstrative way at the Congress of Naturalists at Strasburg (1885). He had introduced into the stomach of a patient with a gastric fistula little muslin bags containing cubes of albumen about the size of hazel-nuts, and after different periods of duration in the stomach these were

withdrawn. The cubes were found to be eaten away in proportion to the time they had remained in the stomach, and when placed in a row made a graduated series like a row of organ pipes. But if dextrine or meat soup, the principal representatives of Schiff's peptogens, were previously introduced into the stomach, the erosion of the cubes occurred much more rapidly, as was easily to be recognised on comparing them with the former series.

I must confess that neither this nor Schiff's earlier statements are surprising, and that they may be better ascribed to a previous secretion of pepsin and hydrochloric acid than to a special "loading" of the glands. We have found that the instant after the introduction of starch solution into the stomach free hydrochloric acid and pepsin make their appearance. This naturally also occurs with Schiff's peptogens, and the subsequent digestion finds ready for it a considerable quantity of hydrochloric acid and pepsin, and can consequently exert a far more energetic action.

The necessary amount of hydrochloric acid in digestive fluids fluctuates within proportionately wide limits, and lies between 0·1 and 5—7 per cent. Moreover, it is not equal for all kinds of food, as we know from the researches of Wawrinsky and Brücke. Fluid albumen is more difficult to digest in feebly acid fluids than solid albumen, whilst the reverse occurs with higher (normal) degrees of acidity. Casein is more easily dissolved than fibrin, the latter more easily than egg albumen, animal albumen more easily than vegetable albumen, differences which obviously depend upon the different capacities of these substances for imbibing hydrochloric acid. Fibrin, for example, when put into hydrochloric acid rapidly becomes a white jelly-like mass, while boiled albumen only becomes transparent in its outer layers and swollen. In this way pepsin takes very different periods to liquefy different kinds of albumen. Blondlot saw that a dog with a gastric fistula digested 100 grms. of boiled albumen in five hours, and 100 grms. of albumen beaten to a froth in three-and-a-half hours. Uffelmann gave a boy with a gastric fistula a solution of albumen and water, and could prove the existence of peptone after twenty minutes; therefore the statement that hard-boiled eggs are digested better than soft, certainly originates in error. Wherever albu-

minoids are taken as constituents of our complexly-formed nutriment, their rapidity of digestion depends naturally entirely upon the condition of the nutriment, that is, its accessibility to the gastric juice. Here is a table in which you will find these conditions arranged, as they are of the highest importance to us as practitioners. (See the end of this lecture.) We know besides that we can digest artificially not only with hydrochloric acid, but also with phosphoric acid, sulphuric acid, acetic acid, and lactic acid, but that the active degree of acidity varies with the acid employed. Davidson and Dieterich in 1860 showed by comparative observations that the same digestion requires with lactic acid about six times higher acidity than with hydrochloric acid, and about half as much again as with acetic acid; 100 grms. of fresh gastric juice dissolve 5 grms. of dried albumen, according to Lehmann; according to Bidder and Schmidt, 2·2 grms.; according to Corvisart, 4·9 grms.

It is not unimportant to remark with reference to the recently much-discussed question of the presence or absence of free hydrochloric acid in cancer of the stomach, that free acid is not necessary to peptic digestion, but that the acid imbibed by the albumen suffices. In my above-quoted work on the coefficient of partage, I have related some experiments which prove this beyond doubt. If, for example, we wash some fibrin and hydrochloric acid jelly with water until the acid reaction disappears, and then add to it some glycerine stomach extract, we get a peptonisation of the fibrin, which, if not so productive as in the presence of free acid, yet removes all objection to the above statement. A. Herzen has arrived at the same result in another way by introducing pieces of albumen through a gastric fistula. Neutralisation of the gastric juice or admixture of bile stops digestion. The latter, according to Burkart, forms a precipitate by means of the bile acids, which mechanically throws down the pepsin; certainly it would need for that a great quantity of bile. A little bile allows the digestion to continue, as you may perceive here. In the earlier editions of these lectures I wrote: "It appears to me doubtful whether the entrance of bile into the duodenum at once stops the pepsin digestion in the chyme; at any rate, small quantities of bile easily find their way into the stomach, as I have often observed, without effect on the gastric digestion." Since then

Boas has directly confirmed this statement by obtaining bile from living men by manual expression (massage) of the duodenal contents into the stomach, and thence withdrawing it by a tube and mixing it with digesting stomach contents. In the mixture of gastric and intestinal juice, a thick copious precipitate is formed, but the supernatant fluid exhibits as before good peptic digestibility. The gastric digestion is hindered or prolonged by all salts of the heavy metals (acetate of lead, mercuric chloride, &c.); hence the well-known rule to administer these considerably before or after meal-times. The influence of preparations of iron is an extremely important chapter in therapeutics, because we so often have to order iron in affections of the stomach; it has been studied by Düsterhoff, and the empirical doctrine that salts of iron interfere with digestion confirmed by him, with the limitation that this occurs less with the proto salts than with the per salts. Salicylic acid, alcohol, carbolic acid, and concentrated solutions of alkalies, have a similar influence, because, partly by irritating the mucous membrane, they give rise to an alkaline transudation into the stomach. Of much importance is the action of alcoholic drinks, the consumption of which, especially of beer, has lately increased so alarmingly. Different investigators—Klikowicz, Bikfalvi, Ogáta, Schellhaas, Schütz—have come to the conclusion, partly by artificial digestion, partly by observations in cases of fistula, partly by experiments made with this object on healthy men, that alcoholic drinks retard digestion, although they are rather at variance as to the required dose of alcohol, inasmuch as some (Ogáta, Bikfalvi, Schütz) put it at 2 per cent., the others at 10 per cent. and more. However, wine even in relatively large quantities (Schellhaas permits half a litre of wine to be taken at dinner) interferes with digestion very little or not at all. The worst enemy of digestion is schnaps, or spirits; if it apparently does good, it does so only because the brain is deceived by the alcohol as to the state of the stomach. Upon the action of neutral salts, which on account of their presence in the various mineral waters have no slight importance for the question of gastric digestion, we have recently had a series of experiments with artificial digestive mixtures, according to which they are all at least not favourable. E. Pfeiffer says that digestion proceeds best without the addition of any salt; it is least controlled by sulphate

of magnesia and sulphate of soda, much more by carbonate and chloride of sodium. Herzen came to an equally unfavourable conclusion as to the effect of chloride of sodium in his gastrotomised patient (*v. supra*, p. 92), as he found in two series of experiments, which in each case lasted six or seven days, that the amount of hydrochloric acid in the gastric juice, without the addition of salt to the food, amounted to 3·14 per mille, with salt in doses of 5, 40, and 20 grms. it fell to 1·26 per mille.

In the results of such experiments, which we must accept "cum grano salis," much may be due to the reciprocal relations of the bodies present in the digestive mixture and their degree of concentration, which in the human stomach must be changing from minute to minute by the process of absorption. Therefore on these grounds it would be quite a mistake to find any serious objections to the use of certain springs like Wiesbaden, Kissengen, Carlsbad, &c., whose beneficial action on gastric digestion is notorious. Moreover, in these cases the water is not taken with food, their relations are obviously quite different, and are not at all elucidated by such experiments. The much-prized bitters and carminatives, according to Buchheim, and according to the more recent experiments of Tschelzoff and Jaworski, do not further digestion; but spices, on the contrary, as is well known, stimulate secretion. Reichmann has so far modified this statement, that bitter infusions taken during digestion inhibit it, but given on a fasting stomach they lead, after the remedy has disappeared, to an increased secretion with the following supply of food, so that bitters should be taken about half an hour before a meal. Heating destroys the action of the gastric juice, but freezing does not. However, gastric juice may be slowly dried at 50°—55° C. without the residue when taken up with water having lost any of its peptic power. The digestive mixture which I show you now was prepared with a glycerine extract so treated. You see in the filtered solution the characteristic reaction of peptone, and perceive besides that even higher temperatures, as previously described, do not make the ferment inactive.

Finally, just a word or two on the seat of secretion in the stomach, that is to say, whether the fundus only or the pyloric region also secretes active juice. There has been a great dispute waged on this subject, which we happily can pass over,

because it is decided by the following experiment of Heidenhain's: separate the entire pyloric region, preserving the mesentery and vessels from the stomach, bring together the remainder of the stomach and the duodenum, and form a sort of pouch in the abdominal wall out of the separated piece. In the dogs which survive this terrible operation, there forms a fistula which secretes a thick hyaline mucus, which, treated with 0·1 per cent. of hydrochloric acid, digests fibrin vigorously, and curdles milk without forming any acid. But, as you may perhaps recollect, the pyloric glands possess only the "so-called central cells"; so this experiment pleads in favour of the view many times disputed, which Heidenhain has supported by other arguments and by the micro-chemical relations of the cells and their different resistance to dilute hydrochloric acid, that we have in the central cells the pepsin-secreting, and in the parietal cells the acid-secreting part of the gland. The thick mucus which covers the surface of the stomach is derived, especially in the pyloric region, from a mucous metamorphosis of the epithelium.

Swiecicki and Sehrwald have given further support to Heidenhain's view of the function of the different kinds of cells. The former showed that in the stomach of the frog, which possesses only parietal cells and no central cells, which latter are only found in the lower part of the pylorus, pieces of meat soon give an acid reaction, but are not digested if the œsophagus is tied. Sehrwald utilised the property of the protosalts of iron to form Turnbull's blue with ferricyanide of potash in acid solutions. If fresh pieces of the gastric mucous membrane were put in such a mixture, the parietal cells became stained a beautiful dark blue, while the central cells inside the glands remained colourless, only the layer lying close under the surface of the mucous membrane showed sometimes a slight blue border, probably in consequence of the entrance of acid gastric juice, in fact, a commencement of *post mortem* digestion.

Table of Gastric Digestion.

Food arranged according to the time required for digestion in the stomach.	Mode of preparation.	Duration in stomach till solution or disappearance.	
		Beaumont.	Richet.
Schnaps	....	....	30′ to 40′
Milk	....	....	30′, 1 h
Cauliflower	....	....	
Cane sugar	....	....	
Bullocks' tripe	roasted	1 h	
Pigs' feet	boiled	1 h	
Rice	,,	1 h	
Peas with butter	....	....	1—2 h 30′
Baked potatoes	....	....	1 h, 2 h 15′, 2 h 30′, 3 h
Whipped eggs	raw	1 h 30′	
Barley broth	boiled	1 h 30′	
Salmon trout	,,	1 h 30′	
Ripe apple	raw	1 h 30′	
Meat (?)	....	....	1 h 30′, 2 h 30′, 4 h, 5 h 30′
Venison	boiled	1 h 45′	
Calves' brains	,,	1 h 45′	
Sago	,,	1 h 45′	
Spinach	,,	....	1 h 45′, 2 h, 4 h
Maccaroni with fat ...	,,	....	1 h 45′, 2 h 30′, 3 h 15′
Eggs	raw	2 h	
Milk	,,	2 h	
Bread	baked	2 h	
Salad	raw	2 h	
Soup with fat and bread	boiled	....	2 h
Rice with fat	,,	....	2 h, 2 h 45′, 3 h, 3 h 15′
Lentils with egg	,,	....	2 h, 2 h 45′
Bullocks' liver	raw	2 h 15′	
Turkey	roasted	2 h 25′	
Pork	boiled	2 h 30′	
Lamb	,,	2 h 30′	
Beans	,,	2 h 30′	2 h
Potatoes	,,	2 h 30′	2 h 30′
Cabbage	,,	2 h 30′	
Cauliflower with fat ...	,,	....	2 h 30′, 2 h 45′
Rice with fat and wine	,,	....	2 h 30′
Maccaroni with fat ...	,,	....	2 h 30′, 3 h 45′
Oysters	raw	3 h	
Mutton	stewed	3 h	

Table of Gastric Digestion—(continued.)

Food arranged according to the time required for digestion in the stomach.	Mode of preparation.	Duration in stomach till solution or disappearance.	
		Beaumont.	Richet.
Soft eggs	boiled	3 h	
Beef-steak	....	3 h	
Ham	boiled	3 h	
Lean bacon	fried	3 h	
White bread	baked	3 h	
Fish	boiled	3 h	
Onion soup	,,	....	3 h
Eggs with sugar	....	....	3 h 30′
Pork	roasted	4 h	
Poultry	,,	4 h	
Veal and Bacon	,,	4 h	
Black bread	baked	4 h	
Cartilage	boiled	4 h	
Cabbage	,,	5 h	
Pork	salted	5 h	
Hard eggs	boiled	5 h	

The statements in these tables are derived from two cases of gastric fistula. The first is the famous Canadian, St. Martin (observed by Dr. Beaumont), who had a fistula in consequence of a gun-shot wound. The second had an impermeable stricture of the œsophagus, resulting from cicatricial contraction after swallowing caustic potash. He was gastrotomised by Verneuil, and afterwards observed by Richet. He obtained food by its being injected through the fistula. The statements in the cases recorded by Schröder, Grunewald, Kretschy, and Uffelmann, are too inexact to be included in this table. The following data, prepared by Dr. Gigglberger, under the direction of Penzoldt, are much more valuable. After he had ascertained that his digestion was thoroughly normal, he tested the time required for the digestion of various meats by introducing a tube into his stomach every quarter-of-an-hour after a meal and expressing a small quantity of the contents. When the stomach appeared to be empty this was determined beyond doubt by washing it out.

	Animal.	Part.	Preparation.	Weight.	Time.
1	veal	brains	boiled	250	2·55
2	—	,,	,,	,,	2·30
3	—	,,	baked	,,	3·05
4	—	sweetbread	boiled	,,	2·30
5	—	joint	roast	,,	3·00
6	—	,,	,,	,,	3·55 (3·30)
7	—	feet	boiled	,,	3·50
8	beef	joint	raw	,,	3·15
9	—	,,	,,	,,	3·00
10	—	,,	boiled	,,	3·30
11	—	,,	,,	,,	4·40
12	—	,,	roast	160	3·15
13	—	loin	,,	225	4·00
14	—	,,	,,	250	3·45
15	—	,,	beefsteak	,,	3·50 (2·50)
16	—	tongue	boiled	,,	3·05
17	—	,,	,,	,,	3·40
18	—	,,	,,	,,	5·00
19	—	,,	smoked	,,	4·15
20	mutton	joint	roast	210	3·30
21	pork	,,	,,	170 (!)	4·00 (3·30)
22	—	,,	,,	160 (!)	2·30
23	—	ham	scraped raw	160 (!)	3·00 (2·30)
24	—	,,	,,	160 (!)	3·10
25	—	,,	raw	160 (!)	4·15
26	—	,,	boiled	160 (!)	3·00
27	hare	back	roast	250 (!)	3·40
28	—	,,	,,	250 (!)	4·25
29	chicken	—	boiled	220 (!)	2·45 (2·20)
30	—	—	roast	230	3·05 (2·35)
31	partridge	—	,,	240	3·30 (2·30)
32	pigeon	—	boiled	220	3·35
33	—	—	,,	260	3·00
34	—	—	roast	195	3·10
35	—	—	,,	210	3·50
36	duck	—	,,	280	4·15
37	goose	—	,,	250	4·00

N.B.—The figures in brackets signify the time at which the muscular fibres had disappeared from the contents of the stomach.

Naturally, such observations give only approximate data. We can easily see from Richet's table, where the same article of food was digested several times, how different may be the period of its

duration in the stomach; but we know also how much the digestion is dependent upon general conditions, psychical influences, &c. Richet justly remarks: "Nul organe, peut-être, n'est aussi fantasque dans sa fonction que l'estomac."

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LECTURE VII.

Gentlemen,—Besides the above described fluid matters, the stomach always contains more or less gas, which consists in part of air swallowed, in part of carbonic acid which proceeds, according to Lehmann, by diffusion from the blood. Planer found in a dog, five hours after feeding, 25·2 volumes CO_2, 68·68 N, and 6·12 O per cent. But according to Strassburg, the carbonic acid tension of the arterial blood is at highest 4—5 vols. per cent., so that the carbonic acid found by Planer could not have proceeded from the blood, but must have been generated in the stomach or intestine. Air is not only carried into the stomach by swallowing, as is certainly proved, but also by coughing or by forced respiration. With the help of a wire œsophagus sound, which served as the electrode of a thermal element, I measured, in the summer of 1876, the temperature of the stomach under different conditions. With every inspiration I observed a diminution, which ceased when the subject of the experiment breathed air at the temperature of the body. How far, under normal conditions, the œsophagus allows air to pass by means of the variations of expansion undergone by the stomach in consequence of the abdominal pressure, I dare not venture to say, as in œsophagotomy we find the lumen of the œsophagus firmly closed.

In healthy individuals the temperature of the empty stomach is higher than that of the axilla, the mean of ten observations making it about 0·6° C. But if the person experimented on breathes deeply, even keeping his mouth shut and breathing only by the nose, great variations occur, in which the temperature of the stomach may sink as far as 0·3° C. below that of the axilla (mean of four observations). Quincke found in a boy of 16, who had a gastric fistula for stenosis of the œsophagus, that the temperature of the stomach measured by a thermometer introduced through the fistula was 0·12° C. higher than that of the rectum. The equalisation of the temperature of variously heated

fluids—water, milk, &c., of $+5°$ C. and $+44°—49°$ C. were introduced—occurred in these experiments for the most part within the first five minutes, and the energy of this equalisation of temperature was so striking that half a litre of water at 5° C. was warmed in less than this time to 19°—20° C. The temperature of milk was raised more slowly. Rodsajewsky had previously performed similar experiments on a gastrotomised patient, and arrived at the following conclusions: After the introduction of food into the stomach the temperature at first falls; this may be down to the absolute temperature of the food, and is so, if the temperature of the food is moderate or low, but is proportional if this is higher. The equalisation of temperature follows slowly, more slowly in the night than in the day, and most quickly at the time when the person experimented upon is accustomed to take food.

Kronecker has taken the absolute temperature of the stomach by means of little mercury balls, which could be swallowed. He found it to be in a fasting dog 38·7°, after feeding with bacon it rose to 40·0°, and also after chemical, mechanical, and even psychical stimuli (showing the dog bacon). The analogy with the relations shown by C. Ludwig of the rise of temperature in the active salivary gland becomes therefore obvious (*v. supra*, p. 37), because it is a general law that organs in action have a higher temperature than those at rest. The subjective sensations which hot or cold food and drink make in the stomach are well known, they are experienced by every one, and under pathological conditions may be very severe and troublesome.

The question of the *self-digestion of the stomach* is of very special interest to us as practitioners with respect to the production of gastric ulcer. Brücke, as is known, has proved that it involves the mucous membrane at right angles to the glands layer by layer, that the acid reaction is only present in the layer immediately next the lumen of the stomach, and that deeper the reaction is neutral or alkaline. Edinger, on the other hand, maintains that the mucous membrane of the fundus, as well as that of the pylorus, is acid. If a solution of alizarin-soda is injected into the blood of a living animal, or a so-called self-injection is effected, all the acid tissues become yellow, and all those which are alkaline become red-violet or red. By such experiments it may be shown that the mucous membrane of a digesting dog is acid

throughout its entire thickness, while in a fasting dog the yellow colour is absent. But these experiments appear to me to prove very little, as it is not clear that a diffusion of stomach contents containing hydrochloric acid may not have taken place into the tissues, and in that way brought about the acid reaction. The experiments of Sehrwald, already described (p. 98), contradict them, especially with reference to this source of fallacy in Edinger's experiments, for they proved that the central cells in the fundus of the gland tubules have an alkaline reaction.

The famous experiment of Bernard—the leg of a living frog thrust into the opening of a gastric fistula in a dog becomes digested—is easy to repeat, especially with a curarised frog. The cadaveric softening of the stomach, or self-digestion, is indisputable. On the other hand, Leube has very lately shown that pieces of mucous membrane may be torn off in sounding or washing out the stomach without any harm resulting. Considerable hæmorrhages into the stomach, obviously from large vessels, occur in many acute febrile diseases without any bad result. Gastric ulcers themselves occur without any definable cause, and extend in breadth and depth very slowly under certain conditions, or frequently heal completely. There is one explanation of this: wherever living blood circulates in the mucous membrane under normal pressure, the gastric juice has no point of attack. But where the normal blood nutrition ceases, either in consequence of embola (Virchow) or of ligature of vessels (Pavy), and necrosis of tissue occurs, there, as elsewhere, the gastric juice digests the dead tissue. Simple hæmorrhages, without distinct fall of blood pressure and slowing of the circulation, are not sufficient, as is evident from many instances of benign hæmorrhages.

The administration of acids, or a simple mechanical lesion, we must maintain, in opposition to Pavy, does not give rise to ulceration. In most cases another factor is present, that is the want of relation between the degree of acidity of the gastric juice and the nutrition of the tissues; it may be that the former is increased immoderately while the cell nutrition remains normal, a so-called hyperacidity resulting, whilst only slight nutritive disturbances exist in the cells; or it may be that the latter, without being actually necrosed, have to such an extent lost their normal resisting power, that in spite of the absence of any increase

in the formation of acid the necessary disproportion between the two factors is effected.

Koch and I, starting from a statement of Schiff's, that certain injuries of the central nervous system are connected with gastric hæmorrhages, divided the cervical cord, or the adjacent portion of the dorsal cord, in six dogs, in order to produce hæmorrhages in combination with diminished blood pressure. As a fact we obtained, in those animals which survived longer than 36 hours, numerous lenticular gastric ulcers, which were mostly circular "and as if punched out," going deeply into the submucosa. With the microscope we could see evidence of hæmorrhage out of the vessels of the mucous membrane between the glands, and in the entire area of the effused blood the elements of the mucous membrane, gland tubules, and connective tissue, were digested deeply down in the shape of a funnel. No traces of inflammatory processes were to be found. The operative procedure produced a deterioration of the nutrition of the tissues, leading to the formation of typical gastric ulcers, and it needs only a glance at the stomach and the preparations which I show you, to recognise the correctness of my statements. Why these hæmorrhages occur, and why only precisely in the gastric mucous membrane, is quite obscure, but according to a case published by McDowall the same conditions occur in man, as a hæmorrhage in the pyloric region led to self-digestion of the stomach, perforation, and erosion of the liver. In opposition to the above-quoted experiment of Bernard's, the carefully shaved paw of a living dog was kept for six hours in a mixture of glycerine gastric extract and hydrochloric acid at the body temperature without being at all affected. Our experiments agree with those of Virchow and Pavy, as it was only when malnutrition of the mucous membrane occurred as a consequence of entire or partial interference with the circulation that ulcerative digestion resulted. This is the reason why ulcers remain so long stationary, and increase so slowly in depth and breadth.

Without going into the other factors for the production of gastric ulcer, as this question will be fully discussed in the second part of this volume, we may here give the experiments of Sehrwald, because they support a view long held by us. This investigator estimated the diffusion power of the living wall of the stomach as compared with the dead wall, by filling a living

stomach tied above and below with a 0·2 per cent. solution of phosphoric anhydride, and noting the changes in this solution which resulted from diffusion; then after the death of the animal he repeated his experiments with the same apparatus after introducing into the vessels through the abdominal aorta a solution of soda, equivalent to about half the alkali contained in the blood. In the latter case the conditions which exist for diffusion in the living stomach were artificially imitated. By special precautions Sehrwald also avoided the fallacy which might arise from allowing the glands in the stomach to secrete. The outcome of these experiments was that the balance between the alkali of the blood and the acid of the stomach contents in the living animal was found not to be in accordance with the laws of diffusion, but much less than it was in the dead gastric mucous membrane, although the conditions in the latter case were much more unfavourable than in the former. The living epithelium must also diminish the amount of alkali given to the blood from the stomach contents, and thereby it does the organism double service, as an economiser of alkali and a protection to the blood, and secondly, as an economiser of hydrochloric acid and protection to the stomach, so that the body is able to economise in a notable degree both in the work of secretion and of absorption. But it is thereby proved that the protection of the stomach is only effectual so long as its cells are living and active. As a lesion of the cell life may occur, either by disturbances of the circulation or by direct lesions of the epithelium, or through disturbances of the trophic nerve influence, we get in Sehrwald's experiments a very valuable experimental basis for one of the above described causes of gastric ulcer, namely, lesions of the epithelium. Still, in spite of all, it remains obscure why these lesions of the epithelium and the formation of ulcers occur only in circumscribed spots, and why their predilection is for particular parts of the mucous membrane. The fact that the gastric juice does not digest living tissue, nor therefore the gastric mucous membrane, we must attribute to the special properties of living cells. Yet it does not remain less wonderful, because the same fact recurs in other places in organic life. Why does not the pancreas digest itself? Why can living molluscs, *e.g.*, *Dolium galea*, produce with impunity a secretion containing free sulphuric acid, while the excised gland is at once destroyed by

it? Here again we have the living cell possessing an immunity against its secretion, just as the torpedo does not feel the shock of its own electrical organ.

In those disorders of the stomach which occasion either an insufficient secretion of acid, or an abnormal delay of the food in the stomach, *fermentative decomposition* in the ingesta arises very easily. The carbohydrates are decomposed ultimately into gas-forming products, and according to the kind of fermentation exciters present—as we have seen in the introduction, they are always brought in from without—sometimes alcoholic or acetic fermentation, sometimes lactic or butyric fermentation develops. The micro-organisms present in the stomach in pathological conditions have been recently investigated very carefully by de Bary and von Miller, but they have come to only slight conclusions relative to their pathogenetic action. De Bary has found quite a number of yeast fungi and schizomycetes, and even the so-called sarcina ventriculi, oidium lactis, bacteria, mucor and flagellate forms, without being able to define precisely their chemical or pathological action, except in a negative direction—that is, that we must not infer the nature of a fermentation from the presence and growth of a yeast fungus, as we are accustomed to do from the analogy of the action of common yeast, whilst the schizomycetes, for example, oidium lactis, certain forms of bacteria, and sarcinæ, undoubtedly give rise to a typical fermentative action. Miller succeeded in cultivating a large series of yeast fungi from the stomach contents of the stomach of a man who was able to empty his stomach at will after ingesting a small quantity of fruit, and who was at the same time not in a normal state of health. These organisms gave rise to intense fermentation, in part with copious development of gas. He succeeded, by feeding a healthy dog with the organisms, in inducing serious digestive disturbances, varying with the composition of the food taken at the same time; in other words, the nutritive media of the organisms influenced in a marked degree the nature of the fermentation, and when he himself finally swallowed a quantity of a test tube cultivation of bacterium ærogenes, he suffered from distension of the stomach with gas and indigestion, which lasted many days.

The first careful exposition of these relations we owe to Frerichs, whose ingenuity transferred the employment of fermentation equations to pathology. In the following table you have

before you the steps of the fermentations in question, and you will at the same time bear in mind the organisms which give rise to them.

$C_6 H_{12} O_6$ Sugar

$2\ (C_2 H_6 O)$ Alcohol + $2\ CO_2$	$2\ (C_3 H_6 O_3)$ Lactic acid
$C_2 H_6 O + O = C_2 H_4 O$ (Aldehyde) + $H_2 O$	$C_4 H_8 O_2 + 2\ CO_2 + H_4$
$C_2 H_4 O + O = C_2 H_4 O_2$ (Acetic acid)	(Butyric acid)

Schultzen and Wilson have shown that many forms of fermentation may occur together. I had the opportunity, in company with my lamented colleague Rupstein, of observing a case in which, as the patient very pithily observed, "there was sometimes a vinegar factory and sometimes a gas-works in his inside." In the one case the alcoholic fermentation led to the formation of acetic acid, in the other the butyric fermentation produced hydrogen and carbonic acid. This patient was specially remarkable, as he at times belched higher hydrocarbons, such as marsh gas, and (perhaps) olefiant gas, which took fire when a light was held in front of him, and burnt with a faintly luminous flame. In this case there must have been present still another fermentation, that of marsh gas. Hoppe-Seyler thinks marsh gas might be regurgitated out of the intestine. Since we know from this observer that an active development of marsh gas takes place from cellulose in sewer mud, it appears to me that the formation of this gas in the stomach is quite possible. A connection between the different fermentations and the kind of food was not proved. The man died later on, and we found that he had not, as we imagined, a dilated stomach, but a flat scirrhous tumour of the pylorus. The shape of the tumour accounted for our failure to detect it by palpation, but it caused decided stricture of the orifice.

But it is not only the carbohydrates which undergo the destructive decompositions in the stomach which we have just sketched. The albuminous bodies also undergo under certain conditions extensive decompositions, which, as we have described in the second lecture, by the action of bacteria lead to the formation of amidic acids, fatty acids, phenol, indol, and other bodies of the aromatic series, in which as products of the tissue metamorphosis of bacteria certain very highly poisonous bodies, ptomaines and toxins, are formed. But this happens only when the reaction

is alkaline, without which the decomposition, which is identical with putrefaction, cannot occur. But in the stomach not only is there normally an acid secretion, so soon as ingesta are brought into it, but the hydrochloric acid has such strong antiseptic properties, and prevents so completely the growth of micro-organisms (Sieber, Miquel, Kast), that some recent authors, *e.g.*, B. Bunge, have regarded its most important property as not its action on peptic digestion but its effect as a bactericide. If this view unquestionably goes beyond the mark, for as already stated I have known a number of persons, some of them for some years, who had no hydrochloric acid in their stomach contents without any putrefactive phenomena being noticeable, it is still unquestionably true that putrefaction occurs only when the formation of free acid in the stomach ceases, and the abnormal delay of the ingesta gives an opportunity for further decompositions to take place. Minkowski has recently explained these relations in a brilliant contribution to the subject of stomach putrefactions, but he has also shown that the stomach is not to be regarded as a completely trustworthy sterilising apparatus, as it can only control within certain limits and guide in definite directions those processes of decomposition which are caused by the micro-organisms which gain entrance with the food, and which develop in part in the stomach, but more especially in the intestine. Moreover, it appears that for this purpose not the hydrochloric acid only but also pepsin plays a part, as the organised bodies become digested by the combined action of both factors. In gastric juice containing hydrochloric acid, in which the pepsin has been destroyed by boiling, an abundant growth of torulæ and bacilli occurs after contamination. Spallanzani long ago observed that pieces of meat put into gastric juice for days did not putrefy. Gastric juice containing hydrochloric acid or gastric contents may be left exposed to the air for a week without decomposition or formation of micro-organisms, whilst if it is feebly acid, neutral, or alkaline, it soon becomes cloudy from micro-organisms and has a putrid smell. We must therefore believe that in disease by absorption of toxins an autointoxication of the patient occurs, and in fact a part of the symptoms of dilatation of the stomach and cessation of the secretion of hydrochloric acid must be attributed to such a process. Certain French authors, Bouchard, Dujardin-Beaumetz, and others,

have expressed this view, and have tried "disinfection" of the stomach and intestine.

When we come to consider the influence of general pathological changes on the secretion of the gastric juice, fever must be placed in the first rank, in accordance with the observations of Beaumont and the experiments of Manassein. In fever, from whatever cause, the gastric secretion does not indeed cease, but obviously a less active juice is secreted. My own experience enables me to confirm this in the most complete manner with respect to the human subject. If we wash out with an equal quantity of water the fasting stomachs of two individuals, one healthy and the other suffering from fever, after having given to each of them, for the purpose of stimulating temporary secretion, a little tinct. capsici, and submit an equal quantity of albumen to the action of an equal quantity of filtered stomach extract from each of the cases, we find that the gastric juice from the fever case digests much less, or at least much more slowly, than that from the healthy person. The reaction is usually acid, rarely neutral: I have only once or twice met with an alkaline reaction. Still we can, as Hoppe-Seyler points out, strengthen digestion by adding hydrochloric acid. This confirms the old practice of prescribing phosphoric or hydrochloric acids in fever mixtures. The diminution of the pepsin digestion is not in all cases equally great, or indeed present at all. In fever patients without distinct dyspepsia Sassezki found no diminution of the digestive activity of the gastric juice. Gluczinski, in a long series of experiments, observed that, generally speaking, in acutely febrile patients the secretion of hydrochloric acid ceased, and the formation of pepsin diminished, but that in chronic fever patients hydrochloric acid may be found. But the secretion of pepsin and hydrochloric acid go hand in hand, so that in the first case there was not a complete cessation, only a diminution of the secretion, to such a degree that free acid was no longer demonstrable. Uffelmann observed in a gastrotomised lad who had chronic fever rising to 39·2° (102·5° F.), that, as above remarked (p. 93), albumen solutions were converted into peptones after twenty minutes, and the boy increased 18—19 per cent. in weight in the course of twelve weeks' fever. In an epidemic of diarrhœa, the same observer examined the vomit of the patients, and found at first, in spite of the fever, that it was actually more acid than normal; but later on the reaction

changed suddenly to alkaline simultaneously with the discharge of slimy bilious masses, and—always an unfavourable sign—the digestive powers thenceforth completely disappeared. On the other hand, the gastric contents sometimes have an alkaline reaction, of course apart from the effects of medicine. This occurs when a strongly alkaline transudation is poured out into the stomach in connection with diminished or entirely abolished secretion of acid.

To these changing or even capricious conditions of production of hydrochloric acid belong the dyspepsias of nervous origin which we see occur as a consequence of great emotional disturbance, or as a chronic disorder, genuine nervous dyspepsia, caused by general nervous conditions. Also reflex dyspepsias may be classed here. Ruff relates, for example, the case of a patient who suffered for some days from complete abolition of the functions of the stomach, but whose appetite and digestive activity suddenly returned after the removal of a plug of wax from his ear.

It is impossible on this occasion to enter into the manifold pathological conditions which give rise to alterations in the chemistry of digestion in the stomach. These relations have recently been studied on all sides, by the help of new methods for the investigation of the functions of the stomach, and are fully discussed in the second part of this volume. Here we may only remark that many diseases may lead under certain conditions to interference with the gastric digestion, with its chemistry, and with the motor functions and absorption of the organ in question. Local changes of its mucous membrane and muscular wall, alterations of its circulation and innervation, direct and indirect, go hand in hand, and result in a variable but more or less definite pathological condition. The insufficient action of one or other of the above-named factors may temporarily be compensated by a greater activity on the part of the other, as, for example, when an insufficient peptic digestion is aided by the rapid transference of the stomach contents to the intestine where the work of digestion is completed.

A very important fact, not only interesting from a physiological point of view, but of the greatest pathological significance, was first demonstrated by the experiments of Ludwig and Ogata on dogs, and afterwards confirmed by Czerny, who kept a dog alive for as long as six years after extirpation of his

stomach. The *post-mortem* examination of this animal showed that there still remained a small piece of the stomach wall enclosing a rounded cavity filled with food, but Ludwig and Ogata in their experiments got complete control of the stomach without extirpating it, by so completely shutting off the pylorus by introducing a uterine dilator into it that no gastric juice could possibly enter the intestine. Food was injected in large quantities directly into the duodenum, and sufficed to maintain the body-weight of the animal. Very remarkable were the changes in the food under these conditions, for while raw minced meat digested well, cooked meat, on the other hand, after a few hours was passed scarcely or not at all changed. Jaworski was the first to draw attention to these conditions from the clinical side, his statements being soon supported by other investigators (Ewald, Rosenheim, &c.).

You will find further information, gentlemen, in the second part of this volume, but here we shall only state that a scientific basis for treatment is to be obtained only by an exact diagnosis of diseases of the stomach, which may be made by a careful chemical investigation of the gastric juice or the stomach contents, the qualitative estimation of its acidity, the testing of the starch digestion, and the action on albuminates, that is, of its peptonising power.

If we desire to examine the chyme, the product of digestion, we may study it in gastric fistulæ, or by the aid of the stomach-pump, or by the method of expression recommended by Boas and myself. Allow me here to describe only some typical constituents. With respect to the greater or less solubility or digestibility of particular articles of diet, I must refer you to the tables at the end of Lecture VI.

Muscular tissues are dissolved more or less rapidly, according to the resistance of their perimysium, their fasciæ, and their accompaniments of fat and tendon, until the gastric juice has only the fibrillæ themselves to deal with. Fat meat is much harder to digest than lean, old than young, raw than cooked. These differences depend upon the solution of the fibrous stroma by cooking and its digestion in the acid gastric juice. The proper pepsin digestion is probably equally rapid for all muscular fibres. They are decomposed into their primitive bundles, and these into a granular mass, in which their finer

structure cannot be recognised. Frerichs says that muscular fibre is never completely dissolved in the stomach; and in fact we find numerous unchanged fibrillæ in the small intestine, as I have recently described in a case of præternatural anus.

Gelatine and gelatine-yielding tissue (cartilage and bone) are very hard to dissolve. If the gelatine is extracted from the bone, it is changed, according to Uffelmann, into a substance very like peptone and sugar. This result of Uffelmann's investigations is all the more welcome, as a long controversy has been waged concerning the fate of gelatine in digestion. Gelatine is very like peptone in its reactions. It does not coagulate on heating, is not precipitated by acids, turns polarised light to the left, but it gelatinises in the cold, and diffuses scarcely at all through animal membranes. Frerichs, Kühne, and Etzinger maintain that the gastric juice abolishes the capacity of gelatine to gelatinise, and according to Hoppe-Seyler it is almost entirely soluble in acids. Uffelmann observed that gelatine, swollen in water, after a long stay in the stomach no longer formed jelly, but diffused easily. It thus approximates very closely to true peptone, with which it agrees also in some of its reactions with precipitating agents. In fact, gelatinous substances are well borne. I can, from my own experience, confirm the good results of the gelatine mixture proposed by Senator as a fever diet.

Milk becomes coagulated, and its fat in part included in the coagula; the casein then peptonises. The latter does not occur if the coagula are removed too quickly, as we see in the well-known white lumps in the diarrhœic or dyspeptic stools of children, which are formed of nothing but fat and casein.

Vegetables, so far as their envelopes of cellulose permit, are easily dissolved and digested. Gums, according to earlier views (Frerichs, Gorop-Besanez) were not digestible. Voit and Uffelmann, however, state that gums and cane sugar are converted into grape sugar, and Leube has shown that human gastric juice converts cane sugar into grape sugar, but the grape sugar is so rapidly removed from the healthy stomach, being probably absorbed, that after a relatively short time no trace of it can be found, whilst under certain pathological conditions this capacity of absorption is absent. The latter appears to be the case in dilatation of the stomach.

The reaction of the chyme must naturally depend chiefly upon the nature of the ingesta, but also is conditioned by the secretion of gastric juice, and varies according to the length of time the food remains in the stomach. If anyone eats a large quantity of organic acids, *e.g.*, vinegar or acid salts, with a meal, the contents of the stomach must have an acid reaction from the first depending upon the substances thus swallowed.

However, this is only an exception, and the acidity depending upon the accidental characters of the food is a matter of subordinate interest.

We are concerned with the curve of the hydrochloric acid secretion of the gastric glands, and the acidity of the chyme which varies with the duration of digestion. The course of such a curve may be very readily constructed. Given a neutral diet, the gastric contents will give an acid reaction only when sufficient acid has been secreted to satisfy the affinities of the albuminates and basic salts in the food, and according to their chemical relations these become converted into acid compounds, or the feebler acids are set free. Then after further secretion free hydrochloric acid appears, the quantity of which "depends upon the strength of the stimulus which the food exerts on the stomach," as Tiedemann and Gmelin, as early as 1825, concluded from their experiments.

Heidenhain found the acid contents of the pure fundus secretion during the first eight hours of digestion to vary very slightly, that is, only between 0·48 and 0·55 per cent. HCl.

Cahn proved in dogs, by careful estimations, that the healthy animal stomach answers to equal stimuli by equal and regular secretion; Rothschild, Hirsch, Penzoldt, and v. Jacksch have studied the acidity curve in the human stomach, and one and all have found that where the food is the same, the course of the curve is identical, so that with a moderate supply of food (Hirsch gave 500 grms. boiled milk, 2 soft eggs, and a white roll; Rothschild gave 200 grms. of pure meat) the maximum was reached about the end of the second hour or the beginning of the third hour, that it lay between 2·3 and 2·8 to 3 per mille HCl, and in the further course of digestion diminished. During the course of this curve, the rapidity with which the maximum is reached varies with different persons, and may vary even with the same individual on different days; the

final degree of acidity, with ordinary diet, appears to lie within the above-named limits, and consequently is, in a manner, regulated by means of secretion, absorption, and expulsion, so that the acidity of the chyme from free acid cannot overstep ever so little this definite limit, just as the alcohol contents of a fermenting fluid cannot surpass a certain maximum figure. Still, this maximum is not absolute, but depends upon the reaction and amount of the diet, as Hirsch found after an unusually heavy midday meal the figure was above 3·0 to 4 per mille in his own case. These figures are, therefore, relative, not absolute.

Finally, gentlemen, we have the question, whether in gastric digestion the albuminous bodies are converted into peptone in the above defined sense, or whether they remain in a preliminary stage, as Kühne's protalbumose or Schmidt-Mulheim's propeptone? That true peptone is formed from albumen by long-continued digestion is, according to the experiments of Kühne and others, not to be doubted, but whether the relatively short time which the albuminous substances remain under normal conditions in the stomach is sufficient for this purpose is not certain. The ordinary biuret-reaction in the presence of peptone is not sufficient to decide this, as our previous remarks have shown, because propeptone, too, gives the characteristic purple colour with copper solution in the cold. The discovery by Kühne, that all previous stages of peptone are precipitated from digestive fluids by ammonium sulphate, makes it possible to settle this question. I have recently performed some experiments with the stomach contents of healthy and diseased persons, both after small and heavy meals, test breakfasts, and ordinary midday meals, in which the contents of the stomach were obtained by means of a tube after one, two, three, and more hours of digestion, so long as any chyme remained. The filtrate was either, after previous removal of the albumen, saturated with powdered ammonium sulphate, or precipitated with saturated ammonium sulphate solution, filtered to remove the salt, evaporated to a small volume, treated with great excess of caustic potash, whereby the ammonia is given off and a precipitate of sulphate of potash occurs. The filtered solution now contains all the peptone which was in the stomach contents, and may be demonstrated by the biuret reaction. *Almost without exception this reaction was very feeble*, being absent altogether in some pathological cases, although in

all cases the freshly expressed gastric contents gave a strong biuret reaction; this difference was the more marked as the latter could have contained only a fraction of the peptone present, while, in the experiment just described, the whole of the peptone must have been collected together. Unfortunately we do not possess any method by which such investigations can be made quantitatively; we are obliged to rely upon an optical examination, which, however, in this case seems so definite that the assertion appears to be justified, that the greater part of the albuminous bodies in the stomach does not generally become converted into peptone.

On the question of the origin of gastric ulcer, Koch and I made six experiments on artificial lowering of blood-pressure by section of the cord, and two in which the lowering of blood-pressure was effected by copious venesection without section of the cord. The former animals had their cords divided at the height of the fourth cervical or second dorsal vertebra, and the animals after the operation were covered up warmly or put into a warm chamber with an inside temperature of 30° C. In the first experiment, we tied at the same time the duodenum at the pylorus and some of the branches of art. gastro-epiploica dextra going to the stomach. The animals were fed in the morning of the experiment with bread and meat, and then, with the exception of Experiment IV., no more food was allowed, but every day 50 to 100 ccm. of hydrochloric acid solution were administered by the œsophagus-tube. All the animals were dead in the course of sixty hours, that is, they either died as a result of the operation, or were killed, as in the case of the dog rendered anæmic by venesection, and that in Experiment I., which was killed. Only one dog with section of the spinal cord lived ten days (Experiment IV.). The anæmic dog had scarcely any changes in his stomach. All the animals with divided cords had typical gastric, and some duodenal ulcers, when they had lived longer than thirty-six hours after the operation. But these were only three out of the six dogs. In these cases the changes were quite characteristic, as shown in the following note from Experiment IV.:—

A middle-sized poodle. On the 17th July, 1878, section of the cervical cord at the level of the seventh vertebra. After the operation, complete paralysis of the lower extremities. The

animal is so lively that it crawls about the room by its fore-legs, barks, &c.; 50 ccm. of hydrochloric acid solution, 2 p.c., daily; eats well. This state continued till July 25th. The dog then became sickly, ate no more, and died on the 28th July. The temperature was normal to the 27th. Autopsy: *stomach contents:* a little thick, brownish red mucus; shows only reddish brown detritus, sometimes aggregated in heaps, sometimes in lumps and punctiform. No muscular fibres, crystals, starch, sarcinæ, vibrios, or other fungi. The stomach contents mixed with a little water and filtered *did not digest fibrin.* *Mucous membrane:* pale, anæmic. From the cardia, especially in the fundus, covered with numerous superficial losses of substance, the size of a pin's-head to a millet-seed, generally round, though sometimes oval or irregularly notched. These were bounded by a thin border of whitish, apparently intact, mucous membrane, sharply contrasting with its surroundings, so that the whole had some resemblance to herpes circinatus. In the proper ulcers the outer ring was more diffuse. The former were often covered with brownish red, easily removable mucus. Only in a few places did the ulceration reach the muscular coat. These ulcers were always at the apices of the folds or on their sides, never at the bottom. About 3 ccm. above the pylorus they were increased in size, especially upon a transversely running fold, where they were deeper, and covered with a dark, blackish brown adherent scab. The largest ulcer, close to the pylorus, was 1·7 cm. long. The duodenum was much injected, the mucous membrane everywhere relaxed. Just below the pylorus were two shallow ulcers the size of peas, similar to those in the stomach. The serous coat of the stomach and intestine was normal. Otherwise nothing particular. Section of cord complete. *Microscopically*, thin sections at right angles to the surface of the stomach, hardened in bichromate of potash and alcohol, showed that the gland tubules in the bloodless ulcers towards the submucosa were eroded away (digested?), without there being any pus corpuscles, fresh connective tissue corpuscles, or other evidence of an inflammatory process. The dark brown scabs already referred to were formed by the blood on the hæmorrhagic ulcers, which was poured out on the floor of cup-shaped ulcers, and lay between the gland tubules and in the submucous tissue. Their origin from a (eroded?) vessel of

the submucosa was very visible in some places. In the deepest places the tubules were quite destroyed; between masses of detritus, blood corpuscles, and remains of intertubular tissue, lay some well-preserved gland cells. In other places the vessels must either have been opened as the ulcer penetrated the mucosa, or the hæmorrhage must have originated in the intertubular vessels, which we saw in such places still covering a remnant of the fundus of the tubules in the submucosa in the entire extent of the ulcer, whilst the bleeding vessel appeared to lie under them in the submucosa. We noted quite analogous appearances in the other two above-named cases. In a quite healthy dog, which for four weeks had daily 50 ccm. of hydrochloric acid solution of 2 p.c., without any result appearing, on the 18th to the 20th August on each occasion about a quarter of the entire blood was drawn from a vein. The dog collapsed and died on August 21st. On dissection, we found the gastric mucous membrane as if tanned; the stomach small, pale, and contracted. On a white, bare-looking, connective tissue-like ground were numerous pale red prominences which resembled urticaria. They were, as shown by microscopical examination, the remains of the proper gland substance. Here a more diffuse superficial erosion was caused by the hydrochloric acid, but no proper ulceration resulted, and obviously it was the chronic excess of acid fluid, so far beyond the physiological proportion, that brought about this change.

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LECTURE VIII.

Gentlemen,—The stay of the chyme in the stomach cannot be stated in precise figures, because the observations respecting it differ widely. Moreover, those on men were made in cases of fistula, in which some pathological influence may have been present. We only know that the stimuli which different ingesta create on the movements of the stomach and the closure of the pylorus, vary according to mechanical and chemical conditions, so that the pressure under which the chyle exists in the stomach is not only, as above remarked, dependent on the muscles of respiration, but directly and in a variable manner upon the contraction of the wall of the stomach. Uffelmann introduced, in such a manner as to be air-tight, a sort of pressure-tube through the fistula into the full stomach of his boy, and saw that the level of the fluid in the tube stood in a varying manner at 2—8½ cm. over the fistulous opening, and showed, in addition to respiratory variations of only a millimetre or so, great risings and fallings which occupied about one minute. These secondary movements are obviously to be regarded as the expressions of the peristaltic contractions of the stomach. But besides this, the fluid in the tube diminished, that is, its level sank gradually lower and lower as the opening of the pylorus (and the absorption of the fluid contents) caused the contents of the stomach to grow less. Schreiber often found in parts negative, in parts a minimum positive pressure, which, however, never exceeded 15 mm. In the case observed by v. Pfungen (a boy with a gastric fistula) the pressure was much higher, this being constantly from 4 to 15 mm. mercury (5·2 to 19·5 cm. water), when the fistula was closed, and varying from the effects of peristalsis between 14 and 35 mm. mercury. The amount was still higher in the antrum pylori, reaching to between 60 and 120 mm., so that the motor power of the body of the stomach was to that of the pyloric portion, on an average as 24 : 77, or under certain conditions as 35 : 120 (vide supra, p. 78). By stretching

and disorganisation of the wall of the stomach, either by immoderate use of food, or by gases, the motor power of the muscular wall is diminished, and the transfer of the chyme into the intestine is delayed. In general, the food remains from one to six hours in healthy stomachs, but under pathological conditions much longer. In healthy dogs we often find the pieces of meat given them on the previous evening still in their stomachs at the following noon, whilst rabbits' stomachs generally do not become empty even after very long fasting. On washing out the stomach, we often find undigested remains which must have lain all day in the stomach. I cannot recall who relates the case in which, during the washing out of the stomach in the spring, grape seeds were found which the patient evidently had not swallowed later than the previous autumn. A similar case has been recorded (1890) by Dr. Krauss, of Mergentheim, since the previous lines were written. In this case a woman aged 60 vomited grape seeds at the end of July, which undoubtedly were derived from grapes eaten during the wine harvest in September or October of the previous year.

We have already described the mechanical processes by which the transfer of the food from the stomach into the intestine is effected, and have explained the new views of Hofmeister, Schutz, and von Pfungen, according to which the chief factor in this part of the motor function of the organ is the contraction of the so-called *antrum pylori*. If a part of the stomach contents do not pass continuously or by short pauses into the duodenum, the constant secretion of the gastric glands (and also the saliva swallowed) must cause an increase in the amount of the gastric contents, unless absorption by the wall of the stomach equalises or more than equalises this addition. But this is not the case. Meade Smith found in the frog, that when the pylorus was closed an enormous accumulation of the stomach contents occurred, and v. Anrep saw the percentage of acid remain the same in dogs where the pylorus was blocked by a uterine tent, although there was evidence of absorption of sugar from the stomach. No important diminution of the fluid contents of the stomach can result, and any loss that may occur with the sugar must be compensated by the secretion into the stomach. If the stomach, under normal conditions, gradually empties itself, this can only happen if the quantity

passing into the duodenum is greater than that secreted by the glands. Of course this process does not go on at the same rate from the beginning to the end of digestion. Although we (Ewald and Boas) observed that 400 cc. solution of starch and 100 cc. of oil lost respectively 220 and 60 cc. in thirty minutes, Cahn found after feeding with 50 grms. powdered meat and 300 water that after thirty minutes there was an increase of about 60 cc., then a decrease, then again an increase, and finally, after two and a half hours a rapid and constant fall in the quantity of fluid in the stomach. So that there is not a constant, but a rhythmical or intermittent discharge, or as has been long accepted by physiologists, a periodical relaxation of the pylorus. How does this come about, and what determines the course of this process? Unfortunately we can answer this question only very inadequately. Doubtless purely mechanical relations, and especially the pressure of the chyme forced forward by the action of the muscular wall of the fundus, are of great influence. But only a definitely altered part of the stomach contents, the chyme, passes normally through the pylorus; so that there must be some selective power which we can attribute only to the physical properties of the stomach contents, to their consistence. They must become pulpy or fluid. If we pour water into the human stomach, we can observe by means of a long stomach tube attached by its free end to a burette, that the level of water in the stomach from the first steadily decreases, and a continuous flow takes place into the intestine. But in the case of digested food we have to do with another important factor, its acidity.

The acidity of the chyme stimulates the muscles of the pylorus, causing tonic contraction, which is only overcome by the muscular contraction of the fundus or of the antrum pylori. This process occurs normally at certain intervals. But it is clear that under pathological conditions, by the derangement of the opposed relations of these two components, disturbances may occur which result most frequently in a delay of the chyme in the stomach, or on the other hand in its abnormally rapid discharge into the intestine.

Most authors incline to the view that the emptying of the stomach contents through the pylorus into the duodenum depends, normally, upon the degree of acidity present. It is obvious that the same kind of food may remain for very varying

periods in the stomach, as Magendie found the gastric contents of horses, fed with equal quantities, varied in equal times after feeding from 1—5 litres.

Busch, in his case of duodenal fistula, saw remains of food swallowed the previous evening appear the next morning, and thinks that the pylorus is generally shut during the night. Many see in the increasing acidity of the stomach the cause of the opening of the pylorus. Kretschy found the maximum acidity in a case of gastric fistula at the seventh hour after eating, and observed, coincidently with the emptying of the stomach, as might be expected, a rapid fall to a neutral reaction. Finally, central influences also play their part, as we have already shown.

It would be of great interest to determine the point of time at which the chyme begins to leave the stomach, and that at which the stomach is empty. The latter has been undertaken by Leube by means of siphoning the stomach contents. It is clear that the fact of the completion of digestion, that is, the proof that all chyme has left the stomach, may be easily acquired in this way. The water poured into the stomach will come back free from cloudiness from remains of food, or with only slight traces if any. At the same time it is certain, that though this experiment permits us to determine the fact that the stomach is empty, let us say six hours after eating, it does not inform us of the exact time at which the last remains of food left the stomach, unless a series of experiments are undertaken beginning with the well-filled stomach and repeated at short intervals until it is completely emptied. But besides the difficulty of getting any-one to consent to such a series of experiments, complications would arise from the irritation caused by the repeated introduction of the tube.

The commencement of the passage of the chyme into the intestine is indicated by the salol test originated by Sievers and myself. Salol is a combination of phenol and salicylic acid, which does not undergo any change in acid fluids, whilst in alkaline media, as well as by the pancreatic juice and by the agency of micro-organisms, principally of the intestinal bacteria, it readily splits up at the temperature of the body into phenol and salicylic acid. Provided that the salol is given at such a time after the food that the acidity of the stomach shall have become well marked, it will become split up only after its entrance with the

chyme into the intestine, and the first appearance of salicylic acid in the urine must indicate the passage of food into the intestine. Sievers and I have for some time recommended the use of salol for this purpose.

It has, in fact, been shown by a series of experiments, and is confirmed by others (Huber, Decker, Brunner, Pal) that the splitting up of salol in the intestine occurs normally 47 to 75 minutes after the ingestion of one gramme of the drug. Unfortunately, even in the same individuals great variations occur within these limits, which alter from day to day, and are explained by circumstances which we cannot control. Bourget has found that this in part depends on the quality of the food, as with pure animal food, taken with a glass of water acidulated with hydrochloric acid, the reaction occurred at the ordinary time, or even about 90 minutes after, whilst with a meal of fruit, meat, and vegetables, it was noticed as soon as from a quarter to half an hour after, which may be accounted for by in the first case a very acid chyme being poured into the intestine, which required a longer time for its neutralisation than a mixed diet rich in organic acids which split up into alkaline products.

One can only say that it is tolerably certain that the passage of the chyme into the intestine begins within the first five quarters of an hour, but it is not possible to be more accurate. Klemperer endeavoured to estimate the motor activity of the stomach by determining how much of a definite quantity of oil introduced into the stomach had disappeared in a given time. In strong and active stomachs 60 to 75 per cent. of the oil is lost, but under pathological conditions it is much less.

Schmidt-Mulheim has made the very interesting observation that the amount of soluble albumen and peptone (obtained by expression of the meat contained in the stomachs of the animals after they were killed) in the stomachs of dogs fed on meat was about the same for the different hours of digestion, so that their removal must proceed *pari passu* with digestion (see also under "absorption" in Lecture XI.), but which process is involved, whether absorption or expulsion, and in what way it works, must freely remain still undecided. Still we know, as above stated, not however with certainty, how and when the closure of the pylorus yields, and the stomach contents make their entrance into the duodenum. Here, obviously, psychical influences play an im-

portant part. These are conditions which in practice often enough play a not very easily determined part, and which find their anatomical basis in the connection of the vagus with the cerebro-spinal centres on the one hand, and the solar plexus on the other.

We pass now to the consideration of *digestion in the small intestine.*

The older authors saw in the small intestine nothing more than a drain-pipe for the chyme, in which the chyle was precipitated by the bile, and in which fat was dissolved and the useless residue passed on for defæcation. We may, without vanity, regard with satisfaction the abundance of new facts which the restless spirit of inquiry of the last decade has disclosed concerning this important subject. Let us commence with the *analysis* of the liver secretion.

I will shorten my task by abstaining from any detailed description of the minute structure of the liver, for which I refer you to the new text-books of Histology. I am permitted to do so, not only from the fact that histology still owes us the answers to the cardinal questions concerning the origin of the bile-ducts, the endings of the nerves, &c., but mainly because the recent investigations concerning the functions of the liver and the part they play in the organism as a whole, have shown most conclusively that the balance inclines much more to the side of general metabolism than to that of the digestive functions. When we hear that dogs with biliary fistulæ, appropriately treated and nourished, remain alive a long time without injury to their general health; when we remember that biliary fistulæ in man exist for years, as in the observations of Fouconneau-Dufresne, Walter, Oppolzer, &c. (quoted in Frerichs' Liver Diseases); that cases of the deepest jaundice may recover without notable injury to the general health—we are sorely tempted to repeat anew, but in reference to digestion, the humorous epitaph with which Bartholinus denied to the liver the Galenic rôle of the blood-preparing organ: "Siste viator, clauditur hoc sub tumulo, qui tumulavit plurimos, &c."

But it is not so; and Blondlot was wrong when, from his observations on dogs with biliary fistulæ, he denied to the bile any share in the work of digestion. The bile has a definite effect in digestive action, but its absence may be compensated for, and, as we have seen, for a long time, by the vicarious

action of other secretions. The liver, from its containing insoluble glycogen, is the mighty storehouse of hydrocarbons for the organism, out of which the blood and tissues are provided as required with grape sugar, just as insoluble starch is deposited in the seeds of plants, which is changed by diastase into soluble sugar and then employed in the nutrition of the cells. It is also the excreting organ for a series of materials circulating in the blood and consumed in the liver, the accumulation of which in the blood, after destruction of the hepatic function, acts poisonously; and it becomes thereby the place of origin of a number of substances which pass in part as urea into the blood, in part as the constituents of bile into the intestine.

But a series of facts indicate that by the formation and excretion of bile we are to perceive much rather the *elimination* from the blood of certain early stages of bile than an essential aid to digestion. The liver has a double rôle. It is an excreting and a storing organ, and its use in digestion, so far as the action of the bile is concerned, is subordinated throughout to the other function. In the pathology of the liver, the absent or altered bile has almost no effect on the digestive process; but it is the derangement arising in the general metabolism which gives rise to the severe symptoms of liver diseases. However, I can only indicate these relations, the discussion of which would lead us too deeply into the region of tissue metabolism, to be consistent with my intention to limit myself to the description of the constituents of the bile and its secretion.

Let us pass on to the description of the bile.

Biliary fistulæ secrete a golden yellow or yellowish green, clear, slightly tenacious secretion of intense bitter taste, feebly alkaline reaction, and a sp. gr. of 1·026 to 1·032—the *bile*. Its quantity increases with digestion, reaches its maximum in the fifth to the eighth hour after food (in Rosenberg's experiments even in the second hour), and then falls again; but the secretion never ceases entirely, except under pathological conditions. Indeed, the starving dogs in S. Rosenberg's experiments secreted an increased quantity of their bile at the hours at which they were formerly used to digest. The pressure under which the bile is secreted is only slight, according to Picard, 50 to 60 mm. water, and the secreting function is here, as elsewhere, dependent upon the circulation, as the ligature of all the hepatic vessels

causes complete stoppage of the biliary secretion. The ligature of the portal vein, with the artery left untied, permits the occurrence of a short continuance of secretion. Slowing of the blood-current in the portal vein, which occurs after stimulation of the vagus as an indirect consequence of slow respiration, and the initially increased blood pressure, causes, according to Heidenhain, a transient increase in the secretion. After diabetic puncture in the floor of the fourth ventricle, B. Naunyn found slowing of the biliary secretion, no doubt as the consequence of the altered vasomotor innervation of the liver, and the resulting diminution in the blood pressure in its vessels. It is possible that these and similar consequences arise in part from the contraction of the smooth muscular fibres of the bile-ducts. Thus a reflex contraction of the bile-ducts occurs when the acid chyme touches the papilla of the ductus choledochus, and Schiff suggests that the chyme as it passes is played upon by a jet of bile. But the whole subject needs more data, and those we have are as uncertain as those concerning the quantity of bile secreted. Thus J. Ranke observed a man with a hydatid of the liver which had ruptured into the lung, who coughed up in 24 hours 652 grms. of bile, but this varied from 145—945 grms. Wittich found in a woman with a biliary fistula 552 grms.; Harley, 600 grms.; Westphalen, 453—566; in dogs, much higher figures are given. The bile formation often appears to be quite suppressed; at least cases are described, like that of von Stabell, in which complete decolorisation of the fæces occurred without jaundice. The action of drugs on the secretion of bile in fasting animals with biliary fistulæ has been studied on an extensive scale by Rutherford and Vignol. According to them corrosive sublimate and calomel in doses of from 0·005 to 0·05 grm. per kilo. of body weight caused increased secretion of bile. Podophyllin and benzoate and salicylate of sodium had the same effect, a conclusion supported by the recent experiments of Paschkis and Rosenberg on the biliary salts of soda and on the bile. In practice I have seen good results following this indication from a combination of podophyllin with cholate of soda. S. Rosenberg has studied in dogs with fistulæ the condition of the bile after the introduction of a large quantity of fat, *e.g.*, 50 to 120 grms. olive oil, and found that its water and solids were both considerably increased.

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On the other hand, it is of some practical value to note that neither the so-called Durande's mixture (turpentine 1 part, ether 3 parts), nor Carlsbad salts had any influence on the secretion worth speaking of.

The composition of the bile may be seen in the following two tables. The first is the mean of two very nearly equal analyses of Frerichs and Gorup-Besanez, which were obtained (1) from a young man of 22; (2) from a man aged 49 (decapitated). The second gives, according to Hoppe-Seyler, the mean of five samples of human bile obtained post mortem, in which only the organic matters are estimated. They amount to somewhat more than half those of Frerichs and Gorup-Besanez; and Westphalen found in the fresh bile of his patient only 2·25 per cent. of solid residue, which by stagnation of the bile rose to 4 per cent. Similar variations are found in other analyses, and it is no wonder, for, as pathologists have long known, the concentration of the bile in the gall-bladder may vary greatly within certain limits.

I.

Water	84·14
Inorganic matter	1·05
Organic matter	15·50
viz.	
Mucus and colouring matter	2·54
Cholesterin and fat	2·95
Salts of bile acids	9·96

II.

Water		91·68
Inorganic matter		
Organic matter		8·32
viz.		
Mucus		1·29
Bile salts	Taurocholate of sodium	0·87
	Glycocholate of sodium	3·03
Soaps		1·39
Cholesterin		0·35
Lecithin		0·53
Fat		0·73

The inorganic constituents consist of phosphates and carbonates of lime and sodium, with potassium and sodium chlorides. Under organic matter, there are still to be named a not yet isolated diastatic ferment, and, according to Naunyn's analysis, sugar. In order to prove *the diastatic capacity of bile*, we must take the fresh bile of an animal just killed. After long standing the bile acts no longer. This property of bile appears to be not constant and to be slight in all cases. Frerichs overlooked it. I have not always found it, which difference I attribute, as just

explained, to changes occurring on exposure to air. On the other hand, Wittich proved its presence in fresh human bile, and indeed extracted the diastatic ferment in question by his glycerine method. If fresh bile is treated with acetic acid its *mucus* is precipitated stained with bile pigment.

We can easily perceive the mucus of the bile, quite apart from its tenacity, in cases of obstruction of the gall-ducts by concretions. There are cases of long-standing jaundice, in which the gall-ducts and the gall-bladder are filled with a pale, mucous, sticky fluid, which scarcely suggests bile. This mucin is in all probability not a product of the liver cells, but a secretion of the bile passages or of their mucous glands, as the more abundantly the bile flows the poorer is it in mucus. But with slow secretion a greater absorption takes place through the walls, which may diminish the percentage of water while increasing the mucus, so that the question as to the seat of the secretion of mucus is as little decided here as in the case of the stomach.

Let us turn to the consideration of the most important constituents of the bile, its specific acids and colouring matter, it being understood that it is not my intention here or elsewhere to enter into details of chemical methods and theories. For our present object that would be only waste of time. Therefore I pass by methods of production, chemical constitution, enumeration of general reactions, &c., and keep to the facts which are important to pathology.

In the bile there are two acids, or rather their alkaline salts, glycocholates and taurocholates of sodium and potassium. They are insoluble in ether, so that they are easily obtained from an alcoholic solution of evaporated bile by precipitation with excess of ether. The fine, acicular, silk-like crystals which you see here, have been separated in this way, and are what was described as Plattner's crystallised bile. If we prepare the acids pure, and boil them with caustic potash or baryta water, they decompose, giving up water, into an acid-like substance, cholic acid and another body which in this case has the character of a base. In one case, this is glycocoll or gelatine sugar; in the other, taurin. The latter is only found in bile, the former is widely distributed in the animal body. Both are nitrogenous substances and direct derivatives of the albuminates. Glycocoll is prepared directly from animal gelatine. Taurin, which is one

of the rarer substances in the organism, may be prepared synthetically from alcohol, sulphuric acid, water, and ammonia, and proves its near relationship with albuminous bodies by containing a considerable quantity of sulphur.

$$\text{Glycocholic acid}\left\{\begin{array}{ll}\text{Glycocoll} & = C_2\,H_5\,NO_2\\ \text{Water} & = H_2\,O\\ \text{Cholic acid} & = C_{24}\,H_{40}\,O_5\end{array}\right\}C_{26}\,H_{43}\,NO_6$$

$$\text{Taurocholic acid}\left\{\begin{array}{ll}\text{Cholic acid} & = C_{24}\,H_{40}\,O_5\\ \text{Water} & = H_2\,O\\ \text{Taurin} & = C_2H_7NSO_3\end{array}\right\}C_{26}\,H_{45}\,NSO_7$$

Of a slightly different composition, according to H. Bayer, is the still little studied cholic acid of human bile, which he calls anthropocholic acid, viz., $C_{18}\,H_{26}\,O_4$; it forms salts just like glycocholic acid and taurocholic acid, giving the same reactions.

Besides these there are hyocholic acid, cheno-taurocholic acid, choleic acid, and fellic acid, which, however, possess a purely chemical interest.

We may mention a reaction of cholic acid with solutions of iodine in iodine of potassium. This is a deep blue coloration, and in the mixture deep blue filiform crystals may be recognised with high powers of the microscope.

Respecting the sulphur in taurin, the sulphur of the bile has some significance; this was found by Spiro, after very careful investigation, to vary very much (from 1·88 to 3·41 per cent.). If taurin is derived from albumen, and the so-called æther-sulphuric acid of the urine has the same origin, it would be interesting to estimate the excretion of each in the same individual for a definite period, and to see whether both were formed in equal quantities from albumen ingested, or whether they were influenced by it or not. Obviously the latter is the case; the sulphuric acid excretion in the taurin of the bile is quite independent of that of the æther-sulphuric acid of the urine, and the two curves are nowise parallel. In other words, great quantities of albumen may be destroyed and excreted in the urine without notably affecting the formation or excretion of taurocholic acid. We know, moreover, other facts which show that the part played by the bile in the processes of tissue metamorphosis is only a very slight and feeble one.

In order to obtain the bile acids by Pettenkofer's reaction,

the biliary salts must be in the purest possible solution. By adding, drop by drop, concentrated sulphuric acid to the solution treated with cane sugar, in time there occurs a gradually deepening purple coloration, provided that the temperature of the fluid does not exceed 70°. The active principle of this reaction has been recognised by Mylius (1887) as furfurol, a body formed by the action of sulphuric acid on sugar. The following method of Strassbürg is of importance for medical practice, as it enables us to ascertain the presence of bile acids in the urine rapidly. Dip a strip of filter paper into the urine treated with sugar, and dry it. A drop of sulphuric acid dabbed on the paper, in the presence of bile acids, becomes after a few seconds a beautiful violet colour, which soon becomes dark purple red, and this detects 0·03 mgrm. of the bile acids with certainty. However, further experience has taught me that this is not always the case; a negative result is indefinite, and in such cases it is necessary to separate the bile acids (by precipitation with acetate of lead and treatment with boiling alcohol).

The pathology of liver diseases has a deep interest in the detection of bile acids in the urine. They played a great rôle for a long time in the questions of hepatogenous and hæmatogenous jaundice, as it was believed that their presence in the urine was a certain criterion of jaundice by absorption. But afterwards, on the one hand, Naunyn found bile acids in the urine of hæmatogenous (pyæmia) jaundice, and he, as well as Höhne, Vogel, and Dragendorff, found bile acids in normal urine, while, on the other hand, Lehmann failed to find them in obstructive jaundice, so that the value of this sign became more than doubtful, whilst recent observations have made the existence of hæmatogenous jaundice, that is, the formation of biliary colouring matter outside the liver, exceedingly doubtful.

The following is a summary of our present tolerably satisfactory knowledge concerning the *bile pigments.*

If we shake bile that has been exposed to the air with chloroform, this takes up a green colouring matter, biliverdin. Fresh bile, however, owes its golden yellow colour to bilirubin, which when pure is an amorphous orange yellow powder, forming, by oxidation in the air or other oxidising means, the green biliverdin (formerly called cholepyrrhin or cholephaïn). Chemists have produced a series of intermediate stages, especially biliprasin

and bilifuscin, and studied their spectroscopic relations and their connections with the pigments of blood and urine, which we referred to in the first lecture. Two points especially interest us: the derivation of and tests for the bile-colouring matter. At first sight there seems no doubt that bile pigment is derived from the pigment of the blood corpuscles, hæmochromogen. By injection into the circulation of a whole series of substances which dissolve the blood corpuscles and set free the pigment from them, we succeed in producing bile-coloured urine. Among these solvents are salts of the biliary acids, solutions of hæmoglobin, large quantities of water, chloroform, and ether, common salt solution, glycerine, toluylendiamine, arseniuretted hydrogen; and in the same way jaundice occurs after burning and scalding, after poisoning with oxalic acid, pyrogallic acid, naphthol, phosphorus, &c.; finally, *icterus neonatorum* and the jaundice that occurs in paroxysmal hæmoglobinuria are both due to destruction of blood corpuscles. The same solution of blood pigment and formation of bile pigment may occur naturally in old blood extravasations, where, as you know, peculiar crystals (Virchow's hæmatoidin crystals) have been found, first by Virchow, later by Hoppe-Seyler, also in the margin of the placenta and in the fluids of cysts, while their identity with bilirubin has been ascertained by Jaffé. Moreover, this formation of bile pigment or bilirubin crystals has been observed in artificial extravasations of blood (Langhans, Quincke), in blood injected into the abdominal cavity (Cordua), in frog's blood kept free from putrefaction (v. Recklinghausen). On the other hand, Funke and Zenker found the same crystals in old bile residue. Valentiner prepared hæmatoidin crystals from pulverised gallstones, and Schwanda succeeded in extracting characteristic crystals from the urine of a case of jaundice. Neumann found bilirubin crystals in the blood of a three-days' old and probably suffocated child. Finally, as before remarked, Hoppe-Seyler has succeeded, by the use of reducing agents, in producing from hæmoglobin a body identical with urobilin, the colouring matter of urine. This urobilin is a derivative of bilirubin, and has been prepared from it by Maly, so that the origin of bile pigment from blood pigment is in fact proved. The bile pigments are only the middle products in a series of reducing processes which convert the blood pigment into the pigment of the urine. It may, in passing, be remarked

here that the question whether the formation of bile pigment can take place outside the liver, and its deposit in the tissues give rise to a certain form of jaundice as a sort of hæmatogenous or anhepatogenous (Quincke) jaundice, is not yet definitely solved, although there is much in favour of the view that though the last stage of formation of the bile pigment takes place in the liver, the material for it may be prepared elsewhere, for example, in the blood by the breaking up of the blood corpuscles. Naunyn and Minkowski were able to demonstrate that geese deprived of their livers and poisoned with arseniuretted hydrogen, which dissolves the blood corpuscles, showed no jaundice, that is, no bile pigment (biliverdin) appeared in the urine, and that when the poisoning preceded the extirpation of the liver the pigment present rapidly diminished without any bile pigment being demonstrable in the blood. Stadelmann also showed that jaundice after poisoning by toluylendiamine was purely hepatogenous, and the same is true of most of the above described measures which give rise to jaundice or the excretion of bile pigment in the urine. Where bile pigment, that is, bilirubin, is found directly in the blood, it is always in dead blood, cut off from the circulation, and not in circulating blood, which may be regarded indeed as anhepatogenous *formation of bile pigment*, but cannot be called anhepatogenous *jaundice;* but Neusser has made some criticisms on the above-described experiments of Naunyn and Stadelmann, which leave the question open as to the exclusively hepatic origin of the bile pigment excreted in these experiments.

This fact has such significance for the pathology of jaundice, that I could not pass it over, although strictly it goes beyond our proper subject. As to the rôle of the bile pigment in digestion we can say nothing, nor do we know how or in what manner it participates in the digestive process, so that I pass to the second of the above points, the reactions of the bile pigment. Respecting this I may incidentally direct your attention to a simple test suggested by Rosenbach: a large quantity of icteric urine is filtered, and the wet filter paper dabbed with a drop of impure nitric acid, at the borders of which comes the play of colours from red to green. Cholesterine (the beautiful shining crystals of which have given rise to the name "bile fat," although this body has nothing to do with fats,

but is an alcohol) and lecithin are bodies about which we are in the same state of ignorance as we are concerning the bile pigment, so we shall be content to remind you of the solubility of the first-named body in solutions of biliary acids and its insolubility in water. Under certain conditions of diminution of the bile-acid constituents of the bile, cholesterine is separated in the form of gallstones.

If we inquire as to the functions of bile in digestion, the few facts we know are quickly enumerated, but their interpretation is uncertain and doubtful. Let us consider shortly what are the contents of the chyme as it enters through the pylorus into the intestine:—

1. All matters still undigested by the saliva and gastric juice, such as starch or paste, gelatinous tissues, dissolved gelatine, albumen (syntonin and native albumen) dissolved by the gastric juice but not yet converted into peptone, and the isolated, partially digested, but still not decomposed primitive muscular bundles. 2. The products of digestion up to the pylorus, viz., peptone, dextrose, lævulose, peptonised gelatine. 3. All matter quite unchanged by saliva and gastric juice, fat, fatty acids, cellulose. 4. Gastric juice or fluid, with the fluid constituents not hitherto absorbed in the stomach, including mucus and gastric juice.

This entire mass possesses a strongly acid reaction. The bile has a very alkaline reaction, and moderates the acidity of the chyme. Many maintain that it neutralises the chyme, and precipitates from the neutral solution the pepsin, syntonin, and unchanged albumen. This is more than doubtful. If we open the duodenum of an animal killed during digestion we find—at least I have always found it so—the contents of intestine beyond the opening of the ductus choledochus still very acid; there is no trace of precipitation of albumen. In the above-mentioned case of præternatural anus I found the reaction of the secretion from the fistula in a much lower part of the gut as often acid as neutral. Schmidt-Mulheim and others have recently found, in complete accordance with this, that the intestinal contents of a recently killed digesting animal have an acid reaction. There can be no good in discussing whether such a precipitation occurs, for, as we shall see later on, the albuminous matter in the mass, as it is precipitated by the changed reaction, is submitted to the

action of the pancreatic juice, which changes it at once into other soluble modifications.

Much more certain is a second property of bile, which it owes to the salts of the bile acids, and which concerns the emulsification of fats. A good emulsion, that is, the finest possible division of the fat-drops in a more or less viscid menstruum, only occurs when the fat to be emulsified contains free fatty acids, and the menstruum has an alkaline reaction. Under these circumstances, as Brücke showed, the slightest shake is sufficient to form a permanent and fine emulsion; indeed, under certain mutual relations between the fat, fatty acids, and an alkali, there scarcely needs, as Gad discovered, any mechanical aid. A drop of cod-liver oil, which always contains some free fatty acids, if placed in a watch-glass with a 0·3 p.c. solution of soda, passes in a few seconds, without any mechanical mixing, by a purely chemico-physical process, into a milk-white emulsion, which, as may be seen under the microscope, consists of the very finest drops. But this takes place only when there exists a quite definite relation of solubility between the soaps formed by the combination of the alkalies present with the fatty acids and the surrounding menstruum, so that the disturbing precipitation of soap membranes is prevented. On account of its alkaline constituents, the bile is capable of forming soaps with the fatty acids; and, secondly, it keeps the soaps so formed in perfect solution. But it is too rich in alkalies to effect this without dilution or partial combination of its alkalies, and under certain conditions it may act so as to prevent the formation of an emulsion. The conditions which are unfavourable to the formation of a good emulsion must be corrected by opposing them, and for this purpose there is abundant opportunity in the intestine. On the one hand, it is necessary to dissolve the little soluble soda and potash soaps, which are derived from the salt and lime of the food, while on the other a too high degree of acidity must be moderated, because both these conditions, as Gad has shown, diminish the goodness of the resulting emulsion. It is certain that the discharge of bile has an influence which, if not very definite, is still very marked. Bidder and Schmidt observed the proportion of the fat in the chyle of two dogs, of which one had a biliary fistula: it was as 32:2. Schwann, and after him others, maintained biliary fistulæ a long time without marked injury to life, but still only, as Voit pointed out,

when the loss of absorbable material was compensated for by increased food. This loss exclusively concerns the fat; whilst in normal animals 99 per cent. of the fat is absorbed, and only 1 per cent. appears in the fæces; in animals with biliary fistulæ, only 40 per cent. is absorbed and 60 per cent. excreted. Rohmann, and especially Fr. Müller, have recently investigated the influence of the exclusion of bile from the intestine on the digestion of various articles of food in the dog and man, by means of careful estimation of the amount of fat and fatty acids in the fæces. Müller concluded that the absorption of starchy matter was scarcely affected at all, that of albumen only slightly, but of fat very much so, as in total exclusion of bile 55 to 78 per cent. of it was found in the fæces, whereas in health only 6·9 to 10·5 per cent. can be found.

Finally, bile possesses an anti-fermentative action, and as the older authors concluded, from observing the hard fæces of jaundiced patients, it is also a purgative. These properties, like many other observations of our acute and observant forefathers, have been fully confirmed by experiment. The bile acids, in fact, act by inducing increased peristalsis, and Rohmann has found, after creating a biliary fistula, an increase of the putrescence of the contents of the bowel and of the excretion of æther-sulphuric acid in the urine, which latter indicates an increase in the intestinal decompositions, whilst Fr. Müller always found in simple icterus that the combined sulphuric acid, as well as the neutral sulphurs, were not importantly altered. For the elucidation of this point further experiments are needed. But you see that all these processes do not consume the bile or modify it importantly, and the question now arises, what becomes of the elements of the bile when they have got into the intestine? A part, *e.g.*, the cholesterine, a fraction of the bile acids and its pigment, indisputably leaves the body with the fæces. But Bidder and Schmidt found in the fæces of five days the constituents of only four grammes of bile, with 0·38 sulphur; whilst, according to an approximative estimate, about 39·5 grammes with 2·37 sulphur were passed into the intestine. Where is the remainder? Schiff long ago suggested that the bile secreted into the bowel underwent a sort of circulation from the intestine through the vessels into the liver and back again into the bowel, the same bile being secreted over and over again. But this

view, like many others of this investigator, has never been properly confirmed, though other observers have found that the introduction of bile or bile acids into the bowels caused an increased flow of bile, while the creation of a biliary fistula and tying the bile ducts caused a diminution of the bile secretion. But the objection remains that an irritation may be set up in the bile apparatus by the destruction of certain constituents of the blood, or that the material for increase may be supplied, especially as the change in the flow of bile, as Rosenberg has pointed out, does not take place suddenly but gradually, whilst it ought to occur as soon as the bile duct is tied. No means exist by which we can trace the injected material, so as to be able to recognise it again, as Schultzen and Nencki, for example, in their famous experiments, found glycocoll depending upon methyl; at least I cannot regard as of great value the experiments of Weiss, who found glycocholic acid, which is normally absent, present in the bile of dogs fed with glycocholate of sodium.

The answer to this question has been nearly reached by means of an interesting series of experiments by Tappeiner. It concerns only the bile acids, which, as I shall premise, hitherto have not been found in the blood, although their presence, when in large quantities, is indicated by the slowing of the pulse. On the other hand, Tappeiner has found them in 150 ccm. of chyle from the thoracic duct, and Draggendorf in non-jaundiced urine. A part, at all events, also passes out of the intestine into the vessels, and it is in the jejunum and ileum that this absorption takes place. This Tappeiner has proved by the aid of an exact method of estimating the bile acids. He injected solutions of known concentration into ligatured portions ot intestine, and after a certain time saw how much had been absorbed. This showed that the solution injected into the ligatured loop of duodenum remained unchanged, whilst in the similarly treated loops of jejunum and ileum absorption had taken place. But even in the jejunum all the bile acids were not taken up by the intestinal epithelium, but only the glycocholate of soda, and Tappeiner makes it probable that the different relations of the particular segments of gut depend upon a specific capacity of their epithelium for the absorption of bile acids.

Milk and bile injected at the same time into a loop of duodenum or jejunum behave very differently. The milk is absorbed

and fills the vessels with milk-white chyle ; the bile, on the other hand, that is, the taurocholate of sodium, remains in the intestine. This experiment, interesting in itself, gains from the latter fact a very special significance for the doctrines of absorption, as we shall see in the proper place.

But this is all we know concerning the function and fate of the bile. Little enough, when we think of the dominating rôle which it at one time played in medicine. Moreover, we know almost nothing as to the pathological changes of the bile in diseases, or of the influence which changed bile exerts on the digestive processes.

The subject of *gallstones* has been most studied. Naturally those who have to do clinically with gallstones and their consequences, know how annoying it is to have the stones not only recognised, but sometimes directly under our hands, and yet to have to remain powerless in their presence. If we know their chemical composition, of which I shall speak directly, we are in the dark completely as to their origin. As most stones consist of cholesterine, which, like bilirubin-calcium, is soluble in bile acids or their salts, we must believe, in order to explain the formation of these concretions, that there is either a diminished production of bile acids, or an increased production of cholesterine. There is still another possibility respecting their formation. If the bile, in consequence of some abnormal process, for example, the increased production of mucus in the gall-bladder, becomes decomposed and acid, or if it stays very long (Thudicum), or remains in the gall-bladder, the easily decomposed glycocholate of sodium splits up into its constituents, forming bilirubin crystals, lime salts, and taurocholate of soda. Chevreuil has advanced for their mode of production the direct proof that more cholesterine is found in bile when gallstones are present. The salts deposit around a little mass of inspissated mucus, or a shred of epithelium, which forms the nucleus of the stone, around which the concretion forms either a homogeneous mass or a laminated or radiated structure. Nine-tenths of all gallstones are formed of cholesterine, they are white or bright yellow, with a shining fracture, radiated or laminated, crystalline, sometimes quite transparent, containing little pigment, sometimes yellowish brown, with a suet-like or waxy lustre on section, and frequently concentrically built up. As a rule cholesterine

constitutes 70 to 80 per cent. of their composition. Hoppe quotes an analysis of Kekulé and Planta, which gave 90·1 to 90·8 per cent. of dry cholesterine, against 4·9 to 5·0 per cent. of loss of weight. Ritter found 98·1 per cent. of cholesterine against 1·5 per cent. organic and 0·4 per cent. inorganic matter. Bilirubin-calcium stones are yellowish red to reddish brown in colour, often chestnut-shaped, with coarse cleavage, and easily reduced to a brown powder which has no fatty feel. Bilifuscin is contained in the small dark grey, almost black, facetted stones, which contain no bilirubin or cholesterine. They consist chiefly of inorganic matter, carbonate of lime, or earthy phosphates. According to Ritter, such stones consist of 64·6 per cent. carbonate of lime, 12·3 per cent. phosphate of lime, 3·4 per cent. ammoniacal phosphate, 0·4 per cent. cholesterine, and 1·4 per cent. bile pigment. Occasionally these substances may be combined differently, and give rise to many varieties. Finally, we meet with cholesterine stones whose surface indicates that a solution of the cholesterine has occurred. This happens by means of soaps and salts of the bile acids, the solvents of cholesterine, when the bile in the gall-bladder is not saturated with cholesterine. We must regard as a sort of psuedo-gallstones those concretions described by Teuffel in isolated and atrophying portions of liver substance.

The few notices concerning the other pathological changes in the bile, such as, for example, the statements of Frerichs, that post mortem there have been found in the gall-bladder albumen in hyperæmia of the liver, and leucin and tyrosin in typhus, have no great significance. In general, changes of the liver parenchyma appear to effect no special change in the bile. I may pass over those changes which are found in closure of the bile-ducts, as well as the excretion by them of certain toxic substances, as not belonging to our subject.

Wiel. Tisch für Magenkrankheiten. Carlsbad, 1877. In this is given the case of grape seeds in a dilated stomach.

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LECTURE IX.

Gentlemen,—If our knowledge of the pancreas had developed in proportion to the zeal which it has evoked from physiologists, it would be the best known gland in the body. Regnier de Graaf, as early as 1662, tied a canula in the pancreatic duct of a sheep to obtain the secretion, but, according to Frerichs, he appears to have been satisfied with the observation of certain superficial characters of the fluid obtained. After him, almost all great physiologists who have worked at the digestive processes, have included the pancreas in their round of investigations. Purkinje and Pappenheim, in 1836, found that the pancreas had a digestive power over albuminoids; but Bernard and Frerichs first succeeded in laying the proper foundation of our present knowledge concerning this gland.

The pancreas is formed on the type of the salivary glands, for the circumstance that the organ has a more extended surface and is not so roundly compressed into the smallest space, so that it has more elongated than rounded acini, makes merely a superficial difference. Therefore, as I may refer you to the description of the salivary glands, I can limit myself to some special points in the changes which the cells undergo during digestion. You may remember that we could distinguish in the cells of the acini of the salivary glands an inner clear mucous layer, and an outer zone with granular protoplasm. The latter is coloured by carmine, and during the activity of the gland spreads over all the cells. Exactly the reverse occurs in the pancreas. Here it is the outer zone of the cells, which lies against the membrana propria, that is homogeneous, clear, and colours with carmine; while the inner layer next the lumen is granular, dark, and not readily stained. The somewhat flattened nuclei lie at the junction of the two layers. During digestion the cells shrink as in the salivary glands, but the granular inner zone disappears gradually, and the clear outer zone extends over the whole acinus, the nuclei becoming round and large. With the aid of a special

apparatus, Kühne and Lea watched by the microscope the delicate rabbit's pancreas in the living animal during digestion: they saw that some tubules were smooth-bordered, others were notched, the latter change being due to the activity of the particular acinus. These investigators could confirm the disappearance of the granular layer, which is described as Bernard's granular layer, as we have stated, following Heidenhain, and we may say with the latter: "During their physiological activity a very extensive exchange takes place in the cells; consumption of matter inside, preparation of matter outside; the inner converting the granules into the secreting elements, the outer employing the nutritive materials to form a homogeneous substance, which on its side, later on, is transformed into granular matter." I can confirm these statements, at least for the two extreme conditions of fasting and digesting animals, although I have not found the distinction between active and passive glands so striking as, for instance, in the stomach. Meanwhile, I will not omit, in reference to the previously discussed question (see p. 35, et seq.) as to the new formation of cells during the activity of the gland, to draw your attention to the fact that neither Kühne nor Heidenhain, the latest and most trustworthy investigators in this region, speak of a new formation of gland cells during digestion. It is probable that the secretion from the cells takes place only in that side of the cells lying next to the lumen of the duct. At least Kühne made the interesting observation that blood corpuscles which get between the cells and the membrana propria when a dilute solution of blood is injected under high pressure into the duct, are not dissolved, whilst they soon disappear in the larger passages. Between the acini of the pancreas there extends a loose connective tissue in which ramify the blood-vessels and nerves. The former surround the individual acini with capillary loops, the latter are distributed as non-medullated fibres in the membrana propria of the tubules. The pancreas is entirely dependent in its function upon the circulation. The gland of a fasting dog is flabby, whitish or yellowish; while during digestion it swells and has a beautiful rosy colour. Here, too, during the activity of the gland the venous blood runs out of a bright arterial red colour, and, according to Kühne, there occurs a capillary and venous pulse, with dilatation of the capillaries. What nerves serve as bearers of these

digestive influences is meanwhile only incompletely made out, and there is scarcely anything known of their connections with the secreting cells. Bernstein found that centripetal stimulation of the vagus stopped secretion, a fact which harmonises with the discoveries of Weinmann and Bernard that during vomiting the pancreatic secretion stops, whilst peripheral stimulation of the vagus or section of it remains without any effect. If this is so, we should expect to find a system of independent ganglia, such as Goltz describes in the stomach; and as smooth muscular fibres have been as a rule only sparingly seen, the increase of secretion obtained by Kühne by direct faradisation of the gland is probably to be attributed to the stimulus of such ganglia. These things, however, are very difficult to decide, because we are not in a position to observe all the conditions of the pancreatic secretion; and, besides, the gland itself appears to be exceptionally sensitive, and rapidly gives evidence of the slightest irritation by changes in its secretion. In successful fistulæ, a common operation in recent times, but which we cannot discuss here, it is found that the secretion persists apart from digestion, whilst soon after food has been taken a clear, somewhat viscid and slightly gelatinising secretion takes place, the quantity and solid constituents of which vary very much, but so far as the latter are concerned, these generally increase as the secretion diminishes. I have obtained at the same period of digestion in about equally large dogs, fed at the same time, sometimes copious, sometimes quite scanty secretion, without being able to assign any cause for this difference. Still the absolute amount is never very great. Bernstein found in the dog 2—15 ccm. in an hour, but I have never obtained more than at most 5—6 ccm. in the same time. Frerichs, however, could collect 25 ccm. in three-quarters of an hour from an ass. The secretion is moreover, like that of the salivary glands, influenced by certain poisons, and according to the statements of Nussbaum pilocarpine and muscarin increase it, eserine (physostigmin) diminishes it, whilst atropine, which acts so energetically on the salivary glands, has no effect. The secreted fluid is, in my experience, always clear, rather thick, free from colour or smell, and of an alkaline reaction, only clouded at first by the products of the irritation of the duct. Hueter found, in the dilated canal of the pancreatic duct which had been occluded by carcinoma, an accumulation of strongly

active secretion which contained peptone, but no albumen or sugar, and was composed of 24 per cent. solid matter, of which 17·9 per cent. were organic and 6·2 per cent. inorganic. Ellenberger and Hofmeister estimated the water of the pancreatic juice of the horse to amount to 98 per cent.; the organic and inorganic matter, chiefly the chlorides of sodium and potassium, were present in the remainder in equal parts. The quantity of the solid constituents varies from 3—10 per cent., which includes the ordinary inorganic salts, albuminous bodies (?) and the specific ferments of the juice, which stamp it as an entirely special secretion. Of these, the pancreatic juice does not include one, but three, which certainly have not yet been obtained pure, but are recognisable by their actions with the greatest distinctness. They are (1) diastatic, (2) albumen-dissolving, and (3) fat-splitting ferments. Just as in the case of pepsin, the pancreatic ferments, which collectively are called pancreatin, may be extracted from the gland by infusion with water, glycerine, salicylic acid, bicarbonate of soda, &c., the albumen-dissolving and diastatic ferments being most readily obtained; the fat-splitting ferment is more difficult to prepare, and seems to be easily decomposed. By precipitation with alcohol and drying the precipitate, we obtain the ferments in the form of a white amorphous powder.

Concerning the diastatic ferment, which was already known to Valentin and Frerichs, we know only that it is equalled, not to say excelled, in activity by no other ferment. The smallest amount of fresh pancreatic juice at the body temperature changes starch paste almost immediately into sugar, or rather into dextrine, maltose, and (a little) sugar. Cane sugar, and a nearly related hydrocarbon, inulin, do not become changed, as I can confirm for the former. Zweifel and Korrwin failed to find the ferment in the pancreas of newly-born children, but I have been able to obtain a perfectly active extract from the pancreas of a puppy three days old. Purkinje and Pappenheim as early as 1836 stated that the pancreas digested albumen; Claude Bernard first observed that coagulated albumen was dissolved by pancreatic juice; Corvisart established the peptonising properties of the secretion, the relations of which to albuminous bodies were later on studied by many workers, in Germany chiefly by Kühne and Heidenhain. The action of the pancreatic juice on albumens

takes place freely only in alkaline or neutral solutions, slowly and laboriously in feebly acid fluids. Consequently, the albumen does not swell as in acid gastric juice, and become converted into syntonin, but shrinks and remains a longer time coherent, and dissolves after having been previously converted into another modification, globulin, insoluble in water. The final soluble modification is a body resembling pepsin-peptone in all its reactions. So that I can refer you for the details of pancreas peptone to the description already given of stomach peptone.

Kühne has prepared from the pancreatic tissues, by the aid of a very complicated method, a body which he regards as the pure ferment and calls "trypsin." But its purity is doubtful, especially because this "trypsin," according to its reactions as given by Kühne, must be mixed in no small degree with albumen or some nearly related body. However, the albumen-dissolving ferment is now generally designated "trypsin."

According to Kühne, the digestion of albumen by trypsin passes through two stages: in the first, the albumen is converted into peptone; in the second, one-half of the peptone, which he terms "hemi-peptone," is further decomposed in a similar way, while the other remains as "anti-peptone," which undergoes no further change. But this is the place to review the relations of albuminous bodies to these peptic or tryptic processes which have been only briefly referred to earlier. We have already seen that Kühne and his pupils, especially R. Neumeister and Chittenden, who have pursued the same current of investigation as their teacher, find that the products formed in the digestion of albumen by pepsin and hydrochloric acid are distinguished from one another by their behaviour with concentrated hydrochloric acid, saturated solutions of common salt and ammonium sulphate, to dialysis, with weak solutions of acetic acid, and acetic acid saturated with common salt, as well as their solubility on heating and the result of the biuret reaction. Those different, but very closely allied bodies, which we speak of under the common name of albumoses, but which may be divided, as previously stated, into protalbumoses, deutero-albumoses (soluble in distilled water), and heteroalbumoses (insoluble in distilled water)—hetero- and protalbumose precipitated by common salt in neutral solution, deuteroalbumose

by common salt and acidulation—are converted into peptone both by peptic and tryptic digestion, and up to the present, as I have already remarked, no chemical or physical reaction has so far been discovered to differentiate the peptones so formed. They are distinguished in no way from the peptones formed directly by trypsin from albumen, without any previous gastric digestion.

However, peptones, like albumoses, may be divided into two groups, distinguished by their varying resistance to certain chemical actions, some being readily transformed by prolonged digestion into further products of conversion, such as amidic acid, leucin, and tyrosin, the others remaining unchanged. This has led to the view, already suggested by the investigations of Meissner and Schutzenberger, that in the peptonisation of albuminous bodies a splitting up of the albumen molecule takes place, forming two different portions, one more resistant and one easily decomposed, of which the first is called by Kühne the anti-group, the second the hemi-group; so that there exists in the albumen molecule one component to be described as hemi-albumen, another as anti-albumen, out of which are derived both series, the hemi-albumoses and hemi-peptones, and the anti-albumoses and anti-peptones. The hemi-albumoses comprise the above-named proto- deutero- and heteroalbumoses. By digestion with pepsin and hydrochloric acid, however, an anti-albumose is also formed, that is, a body which by further peptic digestion becomes an anti-peptone. But if these anti-albumoses are submitted to tryptic digestion, they form next a body called anti-albumide, which is affected very little or not at all by gastric juice, but, nevertheless, becomes anti-peptone; consequently, this anti-albumose allows itself to be converted into anti-peptone in two ways, by peptic and by tryptic digestion, but in each of these ways by means of other intermediate products. In the products of prolonged gastric digestion we find hemi-peptone as well as anti-peptone, so that Kühne has described this mixture as *amphopeptone*.

Not space only, gentlemen, forbids me to go further into these conditions, for these investigations are chiefly interesting from a physiological point of view, and consist rather of the views of one very eminent investigator than of generally recognised facts. What has been said should suffice to give

you some acquaintance with these views and theories when you meet with them in the course of your reading. So much is certain, that the pancreatic digestion is not concluded with the formation of peptones. If we mix an albuminate, or, best of all, fibrine, with pancreatic juice or gland extract at the body temperature, and salicylic acid solution, with the addition of 1 per cent. thymol—which, as Kühne has shown, does not specially injure the action of trypsin—according to the activity of the extract employed we find after a longer or shorter time other bodies together with the peptones. These one would at first ascribe to putrefaction of the albumen, but the digesting mixture shows nowhere any trace of putrefaction by smell or contents (bacteria, vibriones). These bodies are leucin, tyrosin, hypoxanthin, asparaginic acid, and cinnamic acid. On the other hand, if we have employed a feebly alkaline or neutral solution, we soon find a faint putrefactive odour, with development of bacteria and other signs of putrefaction, and, in addition to the above-named substances, the further products of putrefaction, albumen, ammonia, sulphuretted hydrogen, hydrogen, and carbonic acid. It is not easy to decide clearly in this case when putrefaction begins and the normal digestion ceases, unless we can employ, as Hüfner has done, quite special precautions and preservatives against the entrance of putrefactive organisms. But while excluding all putrefactive ferments, he obtained peptone, leucin, and tyrosin—he did not look for hypoxanthin, asparaginic acid, and further products—as the result of the normal physiological pancreatic digestion, to which, according to other authors, hypoxanthin, asparaginic acid, and cinnamic acid (Salkowski, Salomon) may be added. Hüfner also succeeded by another means in proving the same bodies to be products of the physiological pancreatic digestion, and therefore the remarkable fact is made certain, that those bodies which we meet with in ordinary putrefaction of albumen, and which we may derive by chemical agents from fresh albumen, are formed by the normal action of "trypsin."

Nencki has performed similar experiments with gelatine to those of Hüfner with albumen, and has proved the formation of gelatine-peptone, which in its reactions scarcely differs from albumen peptone, as well as the formation of glycocoll, gelatine-sugar, a body formed in the decomposition of gelatine by

sulphuric acid. The pancreatic digestion in the intestine, as in the retort of the chemist, does not remain stationary at the "normal digestive products," but tends more or less to form the so-called putrefactive products which we shall repeatedly meet with in the description of the digestion in the small and large intestine. If I were to give you a table of the action of the pancreas on albumen and gelatine, similar to that for pepsin, leaving out chemical details and accepting Kühne's views, it would take the following shape:—

Albumen + Trypsin (Pancreatin) + Soda Solution of 1 per cent. form at the body temperature first Globulin insoluble in water, and then

Hemipeptone — Antipeptone

Normal Digestive Products	Leucin	Indol	Putrefactive Products
	Tyrosin	Phenol	
	Hypoxanthin	Fatty Acids	
	Asparaginic Acid	Ammonia	
	Glycocoll	Sulph. Hydr.	
		Hydrogen	
		Carbonic Acid	

It scarcely needs to be mentioned that the occurrence of the bodies described as products of putrefaction is contemporaneous with the development of bacteria and micrococci, and is an almost universally admitted result of them. These organisms are taken up with the food, and find in the intestine a favourable nidus for their development. It is certain they are not pre-formed in the tissues, as some maintain, but when they are found, as by Nencki in fresh pancreas, they have got in by chance from the intestine. I have often examined the fresh pancreas of dogs and rabbits just killed, and have never found bacteria or micrococci. The experiments of Hüfner, already referred to, show, moreover, that these bodies have absolutely nothing to do with the products of pure pancreatic digestion, so far at least as concerns the formation of leucin and tyrosin.

There is a remarkable observation of Liversedge, that a pancreas completely exhausted by glycerine, after exposure for some time to the air, again yields an active diastatic glycerine extract. He concludes: "That there is in the pancreas a substance inactive in itself, but which is converted by a process

of decomposition into a ferment," just as the glycogen of the liver, after the death of the animal, is converted into sugar. Heidenhain found further that the glycerine extract of fresh pancreas contained only a trace of the albumen-digesting ferment, but, on the contrary, a body which in a watery infusion of the gland or by simple exposure to the air changed into the active ferment. He called it "zymogen," after analogy with glycogen, that is, the preceding stage of the ferment pre-formed in the pancreas, but not yet forming the actual ferment. He and his pupil Lewaschew have proved that it is changed into the specific ferment most easily in warm and acid watery solutions, much slower in neutral or alkaline solutions, and not at all in glycerine.

Ready-formed trypsin appears to be only exceptionally present in the gland, and the active ferment is formed at the moment of secretion, perhaps under the influence of a formation of acid such as is developed in muscle by its action, and as may be believed from the experiments of Podolinsky, by the agency of the oxygen of the blood; otherwise, we know that there is a previous stage of ferments, a zymogen, not only in the submaxillary gland, but in the stomach, where it occurs as propepsin or pepsinogen, and as a previous stage of the rennet ferment. The difference between the latter and the pancreas appears to be that in this only protrypsin is normally present, whilst in the stomach propepsin and pepsin occur together. But we are here in the region of conjecture, because this anomalous type is by no means differentiated with certainty. The process itself is doubtless of deep significance to the vitality of the gland, perhaps a means of limiting the expenditure of its vital action, but we can only frame hypotheses, and can form no definite conclusions. Later on, under absorption, we shall have occasion to return to these inquiries, which unfortunately leave many gaps unfilled, as they have extended only to the tryptic action of the pancreas, and take no account of its fat-splitting and emulsifying functions.

Finally, Lindenberg has made a remarkable statement not in harmony with the property of the pancreas to digest best in alkaline solutions, according to which trypsin digestion, in accordance with the conclusions of other workers, was found to be interfered with or quite prevented in solutions of 0·01 to 0·1

per cent. hydrochloric acid, but was not only not delayed by acetic acid, and especially by lactic acid, but was actually hastened. By the simultaneous use of NaCl, bile and lactic acid up to 0·02 per cent., this action reached its maximum.

As in the intestine great quantities of lactic acid are formed, partly normally, partly abnormally, and as also common salt and bile are present, this condition is of great significance for the action of trypsin. So far as I know, Lindenberg's statements have not at present been confirmed; moreover, Ellenberger and Hofmeister have stated that tryptic digestion is arrested by 0·3 to 0·4 per cent. of lactic acid. The third, *the fat-splitting ferment*, "steapsin," has not yet been isolated, and is only recognisable in the action of the original juice or in an extract of intestine. It is best demonstrated with quite fresh juice and a neutral fat, which has been treated with a few drops of alkaline, slightly violet-coloured alcoholic solution of aniline purple. If we warm the whole some time in a water-bath, the violet solution of fat and alcohol becomes yellow by the formation of fatty acids. Glycerine and a fatty acid are formed according to the following formula, for which I take ordinary fat, or tallow :—

Tristearine + Ferment + Water = Glycerine + Stearic Acid.

$$C_3H_5(C_{17}H_{34}COOH)_3 + 3H_2O = C_3H_5(OH)_3 + (C_{17}H_{35}COOH)_3$$

On the significance of this formation of fatty acids I have already had the opportunity of remarking when speaking of the action of bile. Their formation takes place slower than that of sugar and probably of peptone. Finally, we must consider the emulsifying action of the secretion, which was described and given an important place by Cl. Bernard. We have already considered the emulsification of fat by bile, and the conditions under which it occurs. Saliva, blood serum, and other more or less mucous and viscid fluids emulsify fat, but the results are not stable, the droplets soon running together, and this happens very quickly if an acid or acid gastric juice is added to the emulsion. The pancreatic emulsion alone remains stable in the presence of a strong acid reaction, and as for the formation of a good emulsion, the presence of free fatty acids, as we have seen, is necessary, we see the great importance in this, as well as in other respects to be described later on, of the fat-

splitting ferment of the pancreatic juice. Cl. Bernard assigned to this property of emulsification of fat, a very important value in the digestion of fat. His views, which were subsequently repeatedly attacked and called in question, have recently been entirely confirmed by the careful and thorough experiments of Abelmann, who employed animals in which the pancreas had been completely extirpated.

Many experiments have recently been made with the view to make use of the pancreatic secretion for therapeutic purposes, and quite a number of "pancreatine" preparations have been manufactured claiming to possess sometimes all the properties of pancreatic juice, sometimes only some of them, but always its tryptic action. Unquestionably it would be of great therapeutic value to supplement artificially the failing function of the pancreas, where we can diagnose it, by introducing such "pancreatines" into the intestine. But the difficulty is, as was shown by Kühne and afterwards by myself, that trypsin is destroyed by gastric digestion, whilst it is just this part of the triple pancreas ferment which is best prepared artificially. Engesser believed he had obtained a preparation by pulverising the gland dried *in vacuo*, which contained protrypsin without any trypsin. This would pass unchanged through the stomach, and its action would be developed first in the intestine by conversion into trypsin. This idea is, however, untenable, as his "pancreas powder" is, as I have shown, destroyed by digestion with gastric juice, and the method employed by him of treating it is just the best for converting protrypsin into trypsin. Unna has attempted, by means of his so-called intestinal pills, to introduce trypsin into the duodenum coated with keratine, so as to be proof against the action of the gastric juice. Keratine, the substance of horn, is soluble, not in acid, but in alkaline fluids, so that the coating of keratine would remain unchanged in the stomach, but would be dissolved in the bowels, and the pancreatine (rubbed up with fat) be free to act. This proceeding, though well thought out (I had tried the same thing myself with water-glass) suffers from not one, but two Achilles' heels.

Firstly, the pills imbibe water, in spite of the coating of fat and keratine. After some stay in the warm contents of the stomach they swell up, become torn, and are attacked by the gastric juice.

Secondly, the reaction of the contents of the small intestine is not, as we have seen, always alkaline enough to dissolve the pills in the duodenum, so that I have repeatedly found them as hard as a stone and quite unchanged in the fæces of my patients. If, however, Engesser's powder or Unna's pills appear to benefit the intestinal digestion in many cases, this may be because the insufficient gastric digestion has altered these preparations either very little or not at all. Moreover, there is in the market a "keratinum pepsino paratum," by Merk, which is not affected by acid gastric juice, because it has been previously deprived, by means of pepsin and hydrochloric acid, of every part of it soluble in the stomach. But even in cases where the hydrochloric acid secretion in the stomach was deficient, and the peptic digestion consequently a failure, I have not obtained good results with pancreatic preparations. We allowed two patients suffering from deficiency of hydrochloric acid to take different preparations of pancreatine from different makers after a moderate meal of white bread and water, without observing any improvement in digestion; so that possibly there are other factors which interfere with the action in the stomach of these artificial preparations which digested actively enough in an incubator. In this case, one was a neurasthenic aged thirty; the other was a man aged fifty-three, with commencing cancer of the stomach and a palpable tumour.

Another way in which pancreatine may be employed is by allowing it to digest certain foods in an incubator, and so to prepare a sort of invalid's food. This plan is especially followed by Dr. Roberts of Manchester, and milk peptonised in this way is recommended by him. The milk is diluted with a fourth part of water, some soda, the necessary quantity of pancreatic ferment is added—Roberts employs a "liquor pancreaticus" made by treating fresh pig's pancreas with dilute alcohol—and the whole is allowed to remain at the body temperature for from an hour to an hour and a half. It is then boiled to check further fermentation, when a preparation is obtained of a slightly dull golden colour, with layers of fat on the surface like the cream of fresh milk. The taste is strongly bitter, which may be diminished by adding cream. In the same way we may peptonise gruel, sago, arrowroot, and the like.

By means of Engesser's pancreas powder, I have frequently prepared peptonised milk, and I reported on it at the Balneological Congress in Berlin for 1881. Most patients objected to the bitter taste, and in the long run lost all appetite for it; but this objection is removed with respect to the preparation called "Voltmer's Mother's Milk," now in the market, in which, by the addition of cream, the taste is corrected and could scarcely be distinguished from fresh milk. This preparation may be employed for some time as a substitute for pure milk. Since we possess the peptone preparations of Sanders-Ezn, Adamkiewicz, Kemmerichs and Kochs, Ross and others, there is scarcely any need to prepare peptonised milk. The suggestion of Dobell, to employ the fat-splitting and emulsifying action of the pancreas, appears to be much more useful. For this purpose a fresh well-cleaned pancreas is pounded in a mortar with one and a half times its weight of distilled water, and digested half an hour at the temperature of the body, then poured through a cloth, and the filtrate shaken with oil or fluid fat. In this way an exceedingly fine emulsion is formed, which remains intact after treatment with pepsin and hydrochloric acid for forty-eight hours. I have had no opportunity of experimenting with it, but Robin has stated that the pancreatic infusion made by digesting the fresh pancreas in water, and subsequent filtering, forms when shaken with oil an emulsion which will resist putrefaction for a month, and which is caused by the formation of alkaline compounds of the fatty acids.

You see from all this, gentlemen, that our knowledge of the nature of the pancreas and its juice is not so insignificant, and we are quite in a position to analyse its action. Would it were so with its pathology! But on this point we can only advance vague notions, if we no longer regard the pancreas as the cushion for the full stomach, like Vesalius; or as the cause of hypochondriasis, ague, and other fevers, like Riolan, Sylvius, and Hoffmann. We know certainly some morbid changes in the gland. Thus we know that occlusion of the pancreatic duct, which generally occurs from tumours in the head of the pancreas, rarely from parasites or foreign bodies, may lead to dilatation of the duct, to cyst formation, called, by Virchow, ranula pancreatica, and to atrophy of the gland substance, which Pawlow has recently produced by experimental ligature of the duct. Such

cysts may quite exceptionally attain to an enormous size, one case observed by Bozemann being mistaken for an ovarian tumour, and only in the course of the operation was it discovered that the tumour was connected with the pancreas. A more or less extensive part of the gland substance may become destroyed, chiefly by cancerous new formations or by fatty degeneration, and hæmorrhages result in the substance of the gland, with sudden or gradual death to the individual. Inflammations, abscesses, &c., occur in the gland, but we know actually nothing of the effect of these on digestion or metabolism. As the first consequence of the abolished function of the pancreas, we notice failure to absorb fats. In fact, Brunner saw the intestinal contents dry up and become fatty after extirpation of the pancreas; and Bright noticed, in 1832, a peculiar fatty character of the fæces which occurred in a case of degeneration of the pancreas and ulceration of the duodenum. Similar observations were, later on, again described; for example, recently by Ziehl and Le Nobel. Ziehl states, that in his case, in which there was simultaneous closure of the common bile duct and the pancreatic duct with jaundice, the silver grey fæces presented numberless fat crystals under the microscope, though to the naked eye they looked like ordinary icteric stools. On the other hand, Le Nobel observed that the fæces always contained much fat when fatty food was taken; and Nothnagel, in his extensive investigation of fæces, long ago showed that needles and bundles of fat crystals, and frequently even droplets of fat, are to be seen in quite normal fæces. Moreover it is quite certain that cases are to be observed of degeneration of the pancreas or closure of its duct without fatty alvine evacuations. I myself have published two such cases in a dissertation by Sauter, where the ductus choledochus was closed by a tumour, and the flow of bile into the intestine was prevented. Litten, Hartsen, and Fr. Müller have observed cases of disease of the pancreas without fatty stools. In the two cases described by the last-named author, there was in one case atrophy, in the other a cyst of the head of the pancreas, but in both there was little fat in the fæces. Moreover, this increase of fat in the stools is by no means a necessary attribute of pancreatic diseases, nor has it when present any certain diagnostic value, because the same phenomenon, according to English authors, occurs in

ulceration of the duodenum. The influence of disordered secretion of pancreatic juice on the digestion of starchy matter and meat has only been studied in individual cases and not methodically. Whilst Langendorff, after tying the pancreatic duct in pigeons, found the digestion of carbo-hydrates greatly affected, Fr. Müller in his cases, referred to above, could only find traces of starchy matter in the fæces, and inferred therefrom that the digestion of carbo-hydrates took place normally. On the other hand, he, as well as Le Nobel, found an increase of muscular fibres in the stools, which indicated a limitation of the digestion of albumen. We have obtained a better insight into all these relations by means of the recent experiments of Abelmann in the Strasburg Klinik. We shall see directly that Minkowski and v. Mering have succeeded in keeping dogs alive for weeks after complete extirpation of the pancreas with removal of the entire gland. In one of the animals so operated on, Abelmann carried out a very careful series of feeding experiments with meat, bread, and fat, which gave the following results: In the absence of pancreatic juice, about 44 per cent. of the albumen was absorbed; a little more, namely 54 per cent., was absorbed when a small piece of the gland was preserved, though there could be no direct flow of its secretion into the intestine; but when fresh pig's pancreas was given with the food, it reached 74 to 78 per cent., whilst an artificial preparation, "pancreatinum purum," had no effect. The starch was chiefly absorbed, although a portion, from 20 to 40 per cent., was not converted into sugar. The neutral fats were not absorbed at all, but a steatorrhœa occurred, which must have been caused by the absence of the pancreas, as it disappeared when pig's pancreas was given with the fat. Notwithstanding the fat was split up, to the extent of 30 to 80 per cent., so that he found in the fæces chiefly fatty acids and only a small quantity of soaps, a fact of the greatest significance for the absorption of fat. Emulsions of fat in the shape of soap and gum emulsions were not absorbed; while, on the other hand, natural emulsions, such as milk, were assimilated to the extent of 53 per cent.

These figures were all somewhat more favourable when the pancreas was only partially extirpated, and this is all the more remarkable as the flow of secretion into the intestine was completely excluded. We must accept the possibility that active

agents passed into the intestinal canal by some other way, perhaps by a vicarious excretion with the other intestinal juices. Still, we must maintain a certain reserve in the face of these statements, and hold that, in spite of Abelmann's interesting experiments, the question is still open.

While hitherto there have been as great differences of opinion respecting the relations of the pancreas to glycosuria as to the digestion of fat, the already-mentioned experiments of Minkowski and v. Mering have greatly advanced our knowledge in this respect. Cantani, indeed, long ago ascribed diabetes to a disease of the pancreas. Bright, and afterwards Frerichs (who, even at the time he wrote his "Clinical History of Liver Diseases," had observed out of nine cases of diabetes five with atrophy or fatty degeneration of the pancreas), pointed out the connection between disease of the pancreas and diabetes. Cantani has found in four out of five cases undoubted fatty degeneration and atrophy of the gland, and other observers, of whom I will only mention Lancereaux as the last, have made similar statements.

We must admit that the pancreas has certain connections with diabetes. Some regard the disease of the pancreas as the cause, some as the result. This connection is supported by the relation between the pancreas and the cœliac plexus, especially by an observation of Klebs respecting atrophy of the pancreas, associated with degeneration of a certain number of the ganglion cells of the cœliac plexus. In these clinically-supported theories there are, of course, many gaps, which have been supplied by the above-named observers, who have found that animals surviving a long time after complete extirpation of the pancreas suffered in consequence of the operation from persistent glycosuria, or rather from a condition quite analogous to diabetes, with polyuria, polydipsia, polyphagia, progressive wasting, &c., and an excretion of sugar amounting to as much as 10 per cent. These symptoms did not occur if a small part of the gland, not less than one-tenth of its entire weight, was left behind. These results were not attributable merely to the absence of pancreatic juice from the intestine, as diabetes did not occur after tying the duct, but to a specific, hitherto unknown function of the pancreas upon the intermediate metamorphosis of matter which under normal conditions must stand in some relation to the consumption

of sugar, so that when the gland is removed sugar comes to be excreted.

That these experiments are very significant in respect to the relations of the pancreas to the metamorphosis of sugar needs no special demonstration. The total extirpation of the pancreas has been attempted by Senn and Martinotti, successfully by the latter. But he has not recognised its consequences with respect to the sugar.

Pisenti observed, after tying the pancreatic duct, a diminution of the excretion of indican to a third or even a fifth part of the original amount.

If a febrile temperature is excited in animals with pancreatic fistulæ, the fermentative power of the secretion, according to Stolnikow, increases at first but is later diminished.

In diseases of the pancreas, extraordinarily rapid wasting has been noticed. Here a causal connection may very well exist, although Colin's animals bore extirpation of the pancreas without injury, and Schiff saw artificially induced atrophy of the gland remain without visible results. Meanwhile, with respect to these and all similar experiments, we may urge that they extend over too short a time, and that chronic destruction acts very differently to acute softening. Genuine simple pancreatic degeneration is one of the rarest occurrences. There nearly always are present metastases to the organs adjacent to the gland, which make the connections illusive between these general diseases and the pancreas. Finally, Schiff maintains that the pancreas is definitely and intimately dependent upon the spleen. After extirpation or elimination of the latter, the secretion of active pancreatic juice stops. This view, as I have proved, originates in a complete mistake. Dogs, whose spleens have been extirpated, secrete as before a perfectly efficient secretion. My statements have been confirmed by Heidenhain and Bufalini.

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LECTURE X.

Gentlemen,—With the pancreatic digestion the digestive function of the alimentary canal reaches its highest point. What happens in the long course through the small and large intestine is chiefly directed to the absorption of altered nutriment and the elimination of unused refuse. Numerous glands, it is true, exist in the wall of the intestine, the latest and completest description of which we owe to Schwalbe, but it is not ascertained what and how great a part Brunner's and Lieberkühn's glands, the solitary follicles and Peyer's patches, play in the digestive processes. It is in the nature of things that we cannot investigate the particular secretion of each gland, but only a mixture of them, in the form of the intestinal juice or an infusion of more or less carefully isolated Brunner's glands. I shall give you only a few hints concerning the histological structure of these organs.

Brunner's glands are tubular, much convoluted glands lying in the submucous tissue, and most numerous near the pylorus. They possess membraneless cells with granular contents and elliptical nuclei imbedded in a homogeneous basis substance. In respect to their membrana propria, ducts, blood and lymph vessels, they bear such a close resemblance to the acinous glands, that we may regard them as a mixed type between the tubular and acinous glands, but still, as was first pointed out by Schwalbe and confirmed by Grützner, they possess the greatest resemblance to the pyloric glands in the stomach. During digestion the cells are small and cloudy, during fasting large and clear, so that the same peculiar change dependent upon the functions of the cell occurs in them which we have so repeatedly met with. According to Grützner the large clear cells are full of pepsin, while the small and cloudy cells contain little.

Lieberkühn's glands are also tubular, with membraneless cells having granular contents and a homogeneous basis substance, inclosed in a membrana propria of connective tissue. According to Schwalbe, they differ from Brunner's glands concerning the

course of the tubes and the shape of their cells in some minute details. In these, the proper secreting cells pass up from the fundus close to the lumen of the gland, where their free bases have often quite the appearance of a so-called basal seam set with rodlets, just like the epithelium of the intestinal villi which we shall have to consider later under the processes of absorption. They are distinguished, however, from the last-named elements, as Heidenhain has recently shown, by the presence of numerous figures formed by nuclear division, the so-called mitoses.

Heidenhain finds that Lieberkühn's glands, even to a greater extent in the large intestine than in the small, are infiltrated with typical mucous cells, which disappear when the intestinal mucous membrane is strongly irritated (as by intra-venous injection of pilocarpin, which is always followed by copious thin secretions), and in their stead are found cells resembling in appearance the ordinary gland cells. But here we seem to have to do with only an emptying of the mucus collected in the cells, and not with their destruction and new formation (vide supra, the salivary glands). Moreover, so far as concerns the glands in the large intestine, Klug and Koreck dispute altogether their glandular character, on the ground that they secrete no digestive juice whatever, and declare that they are only invaginations of the mucous membrane designed to increase the absorbing surface in the same way as the villi do in the small intestine. "With fluid intestinal contents, villi projecting into the intestine are in fact the most favourable organs for absorption; but the more solid contents of the large intestine would compress such villi against the wall of the intestine and eventually damage them, so that here the simpler invaginations are better able to increase the absorbing surface and to further absorption of such nutritive material as is not absorbed in the small intestine."

This view is difficult to confirm or refute, at least I do not find that the more recent works on this subject go into it, and even Bizzozero, who has lately been much engaged in the study of the tubular glands of the intestine, has added no new facts to this question.

On the other hand, we know definitely that the solitary glands and Peyer's patches are not a secreting but an absorbing apparatus, which has many analogies with the follicles of the tonsils, the thymus, or the malpighian bodies of the spleen. These

glands are spherical, lying close under the mucous surface, and have a capsule of connective tissue in which numerous round cells and nuclei are imbedded in a generally turbid fluid coagulable by acetic acid, but surrounded by a capillary network sending branches into the follicle. They are, as you know, most abundantly found in the neighbourhood of the ileo-cæcal valve.

Brunner's glands lie so close together in the upper part of the small intestine, that we may regard an infusion of this portion as an extract of them, without fear of its containing much foreign admixture. Such an extract, prepared, according to Grützner, with glycerine or 0·1 per cent. solution of hydrochloric acid, dissolves fibrin readily, and, according to Budge and Krolow, has also a diastatic action, hence the former investigator disputes the complete analogy between Brunner's glands and the pyloric gastric glands. I have prepared only one such extract, acting completely like that of Grützner.

Our knowledge of the innervation of the intestine may be summarised in the following fashion.

In the wall of the intestine there are, as is well known, two great collections of ganglionic matter which are distributed, one in the submucosa, the other between the circular and longitudinal layers of the muscular coat. They are distinguished by the names of Meissner's and Auerbach's plexuses. Drasch was able to follow up fibres springing from Meissner's plexus to Brunner's and Lieberkühn's glands and into the villi, where they are in part distributed like a tree, in part interlaced like a basket; but as to the connection of the nerves with the glands, in their physiological relations, we know very little more than can be learned from an experiment of Moreau's. He placed four ligatures at equal distances upon a piece of intestine, cut all the nerves which went to the middle of these three compartments, and replaced the whole in the abdominal cavity; after a certain time he found the upper and lower loops empty as before, but the middle loop was filled with much fluid—100 grms. in three hours—containing albumen and inorganic salts. This experiment hardly touches the question of the innervation of the glands; it is much more important for the question of diarrhœa. M. Moreau neglected to perform any experiment on the digestive properties of the excreted fluid, although it was quite easy to do so; it is therefore doubtful whether it was simply a transudation from the blood

resulting from paralysis of the vessels, or a secretion of the intestinal glands. I do not know that his experiments have been repeated by others for this purpose.

This is the place to introduce some account of the movements of the intestine in their dependence upon the nervous system. An easily accounted-for uncertainty reigns over this region, the elucidation of which would be of great and practical interest. The study of the intestinal movements in their normal relations is rendered difficult by the deep invasion of the body required in experiments upon them. We do not know for certain how to decide what part of the phenomena observed may be due to the lesion, as the result of accidental but unavoidable injuries. It is now known that every local irritation of an exposed piece of intestine has for its usual consequence a short local wave of contraction or peristaltic movement, which has been explained, when ganglionic plexuses are present in the walls (Auerbach's plexus mesentericus), as a reflex irritation coming from the ganglion cells. The activity of these plexuses can give rise to spontaneous intestinal movements. But it is not quite clearly shown *where* we can produce local contractions. We must either assume the presence of ganglia, as we have done above with reference to Goltz's experiment on the gastric innervation, or, like Engelmann, take refuge in another hypothesis, namely, that the movement of muscle cells originates in themselves. By means of a peculiar observation Nothnagel believes that he has refuted the latter view. If a small crystal of a soda or potash salt is placed upon the exposed intestine, the sodium salt causes a contraction running some centimetres upwards towards the stomach, while the potash salt causes only a quite limited local constriction. But if the nervous apparatus of the intestine is killed in any way, for example, by bleeding or tying the vessels of a loop of intestine, or by poisoning it with morphine, the longitudinal contraction after the application of sodium no longer occurs, and only the local reaction follows. A proof, as Nothnagel thinks, that nervous elements must participate in the former case. But the broader, longer waves are obviously to be ascribed to general causes lying outside the organ. They can be attributed either directly to the terminal nervous apparatus in the intestine, or indirectly to changes in its circulation. It was formerly believed that the movements of the intestine were caused by vascular anæmia, by

obstruction of the aorta (Schiff), or by general changes in the circulation in the intestinal vessels (Donders), while hyperæmia checked the movements (Betz). But this is not altogether correct. Pflüger showed by his famous discovery of the inhibitory power of the splanchnics on the intestinal movements, that, on the contrary, vascular anæmia may be combined with inhibition, and hyperæmia with excitation of peristalsis. Mayer and Basch saw compression of the aorta followed by quieter movement or by stasis of the movements of the intestine. But the constancy of the splanchnic influence cannot be altogether confirmed. It is the same with stimulation of the vagus or artificial hindrance to the respiration, two factors which should equally have peristalsis as a constant result. All these give irregular results, sometimes positive, sometimes negative, sometimes none at all. Pal has quite recently proved by careful researches on this point that opening the abdomen alone checks the movement of the intestine. On the other hand, Braam Houckgeest has endeavoured to get rid of the irritating influence of the atmospheric air in the examination of the exposed intestine, by opening and observing the abdominal cavity of animals under water ($\frac{1}{2}$ per cent. solution of common salt). He confirms Pflüger's statements concerning the splanchnic. Paralysis (*i.e.*, section) of this nerve, which, as you know, is accompanied by hyperæmia of the intestinal vessels, is followed by increased peristalsis, that is, increased activity of the motor elements of the small intestine; while stimulation of the splanchnic, which causes vascular contraction and anæmia, is followed by inhibition of the movements. The vagus, however, influences peristalsis only indirectly, by causing contraction of the stomach, and thereby gives an impulse to the intestinal movements, whilst peristaltic waves may be induced in any part of the intestine without the intervention of the vagus. According to experiments published by Ehrmann from Prof. von Basch's laboratory, the splanchnic and vagus exercise a double and indeed crossed action on the longitudinal and circular muscular fibres, which may be explained by the following diagram :—

Longitudinal fibres moved by the splanchnic	controlled by the vagus
Circular fibres moved by the vagus	controlled by the splanchnic

The motor and inhibitory nerves of the rectum have similar relations, as was proved in the same laboratory by Fellner. But in this case the longitudinal and circular muscular fibres are innervated separately. "The motor nerves for the longitudinal muscles run in a branch of the sacral plexus, anastomosing with the hypogastric plexus, and known as the 'nervus erigens'; and the motor fibres for the circular muscles lie in a pair of nerves which start from the posterior mesenteric ganglion and send branches to the hypogastric plexus." The motor nerves, therefore, exert an inhibiting influence in a crossed fashion. The motor nerves of the longitudinal fibres inhibit the circular fibres, and conversely, so that the motor impulse to one set of muscles has an antagonistic effect on the other. There is good reason for this. If both sets of muscular fibres were to contract at the same time, the lumen of the intestine would be, as one can easily perceive, completely, or nearly completely closed, it would give rise to a stationary contraction of the bowel, and not to progressive waves such as are understood by peristalsis. The latter, moreover, consists much more in combined contraction and relaxation of both sets of muscles, so that one set of fibres comes into action only when the other is at rest. The inhibiting centre for the movements of the bowel, which may be studied after the administration of morphine or opium, according to the experiments of Pal and Bergrün, is situated in the neighbourhood of the lower cervical and upper thoracic cord. Finally, the circulation is so far important that the "pouring out of digestive juices" in any part of the intestine causes spontaneous movements, while anæmia of the intestine always stops or at least enfeebles them. Fubbini and Luzzati have observed in animals with Vella's fistulæ (vide infra), that the movements of the intestine were favoured by the flow of bile, whilst they were slowed by sleep and by low temperatures. A more intimate knowledge of these relations, especially in connection with the influence of varying compositions of the blood, has not yet been gained in spite of many experiments directed to them (Salvioli).

But the intestinal contents, which consist of gases and solid matter, may, by irritating the wall of the intestine, give rise to peristalsis, and in connection with this point the conclusions of Bokai are very interesting, as he repeatedly undertook the

observation of the intestines in warm salt baths, introducing various gases and dissolved matter into different parts. According to him nitrogen and hydrogen are indifferent, on the other hand carbonic acid excites strongly, first peristaltic and then rolling movements of the bowels, which can be limited or cut off by oxygen. Marsh gas and sulphuretted hydrogen act in a similar way, but are much less feebly influenced by oxygen, a result which Bokai compares with the well-known laxative effect of sulphur, and which he attributes to the formation of sulphuretted hydrogen, while on the other hand he ascribes the action of bismuth in controlling diarrhœa to its property of combining with sulphuretted hydrogen. The acids present in fæces, lactic acid, acetic acid, and acids of the fatty series, proved also to be strong stimulants of intestinal movement, the strongest being caprylic and the weakest lactic acid. Of the products of putrefaction, skatol even in small quantities caused very strong peristalsis, while phenol and indol proved indifferent.

Hitherto it has been generally believed that antiperistaltic movements never occur in normal living animals, and as Nothnagel saw, only occur when strongly irritating substances are present in the intestine. This is not correct, as Jacoby has recently seen, for by the employment of better methods which exclude intestinal irritation, he has observed spontaneous antiperistalsis (in cats), not only in the small intestine proper but at the lower end of the ileum, which were not caused by any external irritation caused by the experiment. Kirstein has added another proof of the occurrence of anti-peristalsis, by cutting out a piece of intestine about 57 cm. long and sewing it in again the reverse way. The animals remained alive after the experiments without any special affection, a dog living to seven weeks, when he was killed in perfect health. It follows from these experiments that antiperistalsis must have occurred in the piece of intestine which was resected, or otherwise the intestinal contents could not have passed through it. Still we cannot speak of this as antiperistalsis in a proper pathological sense, and this does not occur in a pronounced fashion in the upper end of a completely tied loop of intestine. These observations are of great importance in connection with ileus and fæcal vomiting. The ancient view formulated by van Swieten, according to which pressure of the abdominal walls and not antiperistalsis drives

the intestinal contents through the stomach, has acquired fresh value. The method of "expression" employed by Boas and myself in the diagnostic examination of the stomach, shows how easily the stomach contents can be expelled by abdominal pressure when the cardiac orifice is open. Horvath's statement is of practical interest, that cold from 0° to 19° causes a prolonged or complete cessation of peristalsis, a fact of which I have made use for some time by injecting cold water into the intestine in the treatment of the diarrhœa of children. Very noteworthy, finally, for the explanation of the therapeutic working of morphine (or opium) would be an observation of Nothnagel's, if confirmed, from which he is led to attribute the constipating effect of morphine to an excitation of the inhibitory nerves of the intestine. He saw the peristalsis caused by sodium salts, which has been already described, cease after relatively small injections of morphia, but return when the piece of intestine in question was severed from the mesentery, and thus separated from its connection with the splanchnic nerve. Apart from the fact that Nothnagel appears to have overlooked the double (crossed) innervation of the intestine (vide supra), it is clear that in this experiment there were alterations in the circulation and local causes of irritation which could have participated quite as much as irritation or inhibition of the nerves leading to the part.

The intestinal juice is best obtained by means of Thiry-Vella's fistulæ. An excised piece of intestine, about 30 to 50 cm. long, still left in connection with the mesentery, is sewn up at one end, while the other is united to the abdominal wound. The continuity of the rest of the intestine is repaired by carefully sewing the ends together. The secretion of these fistulæ, or, as they should rather be called, pieces of intestine, is regarded as normal intestinal juice, but it may be questioned how far the secretion of such a piece of intestine exposed to the air exhibits normal relations, and the following data, upon which there is by no means a desirable amount of harmony, are to be accepted with a certain degree of reserve. This uncertainty is explicable, if we consider how easily after such an operation, quite apart from the irritation to the mucous membrane, vascular alterations may occur which may lead to transudations from the blood, and quantitative or qualitative changes in the fluid

from the fistula. Every one knows who has worked at the intestine and mesentery how extraordinarily irritable the vessels are, and the experiment of Moreau just related is so far evidence of this. Besides, the fistula does not secrete spontaneously, but only upon mechanical irritation or pilocarpine injection. Neither direct irritation of the vagus nor reflex irritation, as by rubbing the abdomen with croton oil, gives rise to secretion. Lehmann found the secretion alkaline, opalescent, clear sherry-coloured, sp. gr. 1017 to 1021, with 3·6 to 4·7 solid matter, of which 1·53 per cent. was organic material. Thiry estimated that a dog in from two to seven hours after feeding secreted in his whole intestine about 350 grms. As to its action, agreement prevails only on one point, namely, that it dissolves fibrin. With respect to the rest, the statements diverge widely, some asserting it to have a fermentative action on other albuminoids or on starch and fat, while others deny these. Bunge regards the chief importance of the reaction of Brunner's and Lieberkühn's glands to be its alkalinity and its component carbonates, by which the excessive acidity of the chyme is neutralised. An observation of Demant's was made on the secretion of a fistula of the ileum, in a patient whose upper intestinal contents were separated from it and emptied by a second fistula; he obtained only a diastatic and inverting ferment in the intestinal juice, but found neither peptonising nor fat-splitting properties in it. Gumilewski was also able to note its strong diastatic properties. On the other hand, Vella, in his animals operated upon (eighteen dogs) proved with certainty the existence of a diastatic emulsifying and glycerine-forming as well as peptonising action. In fact, the intestinal juice, in spite of its alkaline reaction, possesses also the property of curdling milk, as milk injected in at one opening always comes out at the other curdled. You remember, gentlemen, that Kühne and Roberts ascribe to pancreatic juice a kind of rennet action on milk. But in the most recent and careful researches which Rohmann has made upon three dogs with Vella's fistulæ, of which one had a piece of intestine 30 cm. long, there is no question of any milk-curdling action of the intestinal juice, but, on the other hand, the diastatic action is distinct, as it does not only convert starch into sugar, an action which is stronger in the upper sections of the bowel than in the lower, but it converts cane sugar into invert sugar. However, some one should investi-

gate whether *all living tissue in contact with the air* does not possess this feeble diastatic action, and also the power of coagulating casein. So much is certain, that even the dried intestinal mucous membrane cut into small pieces inverts cane sugar, and can transform dextrine into maltose (Brown and Heron, Ewald), and the majority of authors have affirmed the diastatic action of the intestinal juice. But the statements are very contradictory, and I will therefore not weary you with further details of the discussion. Boas has recently described a method for obtaining the intestinal juice, or, more properly speaking, the intestinal contents, of living human beings not operated on. It is possible in many persons to press back the contents of the duodenum into the stomach, and to obtain these by means of the stomach tube. No doubt, according to the fulness and the irritability of the stomach, these are more or less mixed with the stomach contents or gastric juice, and, according to the stage of digestion, the expressed material must consist of a mixture of bile, pancreatic juice, intestinal juice, the digested products of the stomach, and that still undigested. It is clear that such a product can afford no certain conclusions as to the action of pure intestinal juice, and its main interest consists in the possibility of observing how far these different juices antagonise one another. We shall return to this question later on. As in the large intestine either none or only traces of a digestive fluid are secreted, and the absorbing function of the intestine becomes almost its exclusive business, we can, so soon as we have considered the constitution of the intestinal contents, in so far as they are still preserved, approach the most important and prominent peculiarity of the intestinal mucous membrane, its absorbing function.

The chyme, the composition of which we have described at its entrance into the intestine, becomes altered as it passes down the intestine in its chemical and physical relations in the following manner: the reaction becomes alkaline or at least neutral in the jejunum, as in my case before alluded to, while it seems, according to the observations of Schmidt-Mulheim, J. Munk, and Cash, that in dogs it may be acid from first to last. In the ileum, even in man, it becomes acid from the formation of acids from the putrefaction of albumen and fermentative processes. The substances which we have already learnt to recognise as the products of putrefaction, are in fact all, or nearly all, present in the lower

part of the alimentary canal, and owe their existence obviously to the same putrefactive processes as produce them outside the animal body, only that, favoured here by the natural conditions, they proceed more actively than elsewhere, and are accompanied by fermentative processes which lead to the formation of lactic acid, butyric acid, &c. I have only to refer you to the formulæ which I showed you previously (pp. 27 and 151) for these processes, for you to have at one glance the whole of these bodies before your eyes. If you recall at the same time the obscure proposition of the iatro-chemical school related in the introductory Lecture, which made the digestion a putrefactive process, these remarkable facts acquire in themselves an increased interest, and we are reminded of an apt remark of Du Bois Reymond's that the curve of scientific opinion always comes back after a certain time to its starting-point.

Besides the products of putrefaction which belong to the so-called aromatic substances, and besides the so-called ptomaines, whose importance and significance we have already studied, there are particularly two of these bodies which have excited in recent times an overwhelming amount of attention. Indol ($C_7NH_6\overline{C}H$), first found by W. Kühne in bacterial putrefaction, and phenol ($C_6H_5\overline{O}H$), or its homologues ortho- and paracresol, which was discovered by Baumann in putrid albumen, and by Brieger directly in human fæces. Both appear in the urine by absorption from the intestine. Indol is oxidised to indoxyl, and this combines with sulphuric acid and potash to form potassium indoxyl sulphate, or indican, the mother substance of that pigment which gives the urine a blue colour on the addition of hydrochloric acid and solution of chloride of lime (calcium hypochlorite), that is to say, the indican in the presence of oxidising agents splits up into indigo blue and potassium sulphate, and the test for indican in the urine is based upon this reaction. Phenol or cresol combines after its absorption from the bowel with sulphuric acid, and appears for the most part as phenol-sulphuric acid in the urine. Both are dependent for their occurrence and their quantity upon the intensity of the putrefaction going on in the intestine and the rapidity of the movements of the intestinal contents or their stay in the lower portion of the canal.

The quantity of phenol excreted in the urine amounts normally, according to J. Munk, to 0·017 to 0·051 grms., but according to

Brieger may reach as high as 0·6 grms. Normal human urine, according to Jaffé, is very poor in indican (6·6 mgrms. to the litre), an amount which is greatly increased only in pathological conditions, occlusion of the small intestine, internal hernias, carcinoma, &c., that is, processes which lead to stasis of the intestinal contents and to proportionally greater decomposition. But these, like all the bodies belonging to this group, have scarcely anything to do with the true digestive and nutritive processes. In cases like that of mine, where the lower part of the ileum and the large intestine were as good as completely closed, and the entire intestinal contents down to the fistula, which was probably seated in the lower third of the ileum, were discharged by it, these substances were completely absent, only returning when the connection between the upper and lower intestine was renewed by operation. Still the nutrition of the patient proceeded well, and, considering the general derangement, was particularly good. Indol and phenol are allied products, which the body gets rid of as waste through two channels, the kidneys and the intestine, whilst they own their formation, as above remarked, exclusively to putrefactive processes in the contents of the bowel. E. Baumann, by preventing these processes by large doses of calomel, was able, in complete accordance with my above related observation, to notice the complete absence of aromatic substances from the urine, and Kast and Wasbutzki have estimated the excretion of ether-sulphuric acid as the direct measure of the putrefactive processes in the bowel, and the effect produced on them by the free acids of the gastric juice. But these are processes of a universal nature, and the hopes have not been confirmed which were first raised by Jaffé's experiments, that close connections might be formed between pathological conditions of the intestine and the excretion of these bodies. Senator, whom I can completely confirm from my own experience, has drawn attention to the inconstancy in the amount of indican excreted. These statements have since been confirmed by Hennigs and Nothnagel. The same, according to Brieger, is true of phenol, and when we consider how many factors participate in the excretion of these substances—food, rapidity of peristalsis, intensity of putrefaction, amount of absorption—we cannot be surprised at this.

But if we turn away from this practical point, it is certainly

very interesting that phenol, which we make use of extensively every day for its antiseptic properties, should be found as a product of putrefaction, and that actually in our own intestines!

The intestinal gases, the formation of which is explained by the table of fermentations, consist of carbonic acid, hydrogen, nitrogen, sulphuretted hydrogen, and marsh gas, which last is formed by a special fermentation, marsh gas fermentation, the substratum of which exists in the cellulose taken with vegetable food. These amounts vary very much, being in part dependent upon the diet—I may remind you of the flatulence following ingestion of certainly easily fermentable vegetables, cabbages, &c.—in part on the absorption of gases formed in the blood. A great part, indeed the principal portion of the intestinal gases are, as Professor Zuntz has proved by the interesting work of his pupil Tacke, taken up at once into the blood and eliminated in the expired air through the lungs. It was shown in one experiment (made on rabbits) that whilst in two hours 2·1 ccm. of gas were got rid of by the anus, 16·7 ccm. of hydrogen and carburetted hydrogen were discharged by the lungs; and in another, whilst during ten hours forty-five minutes 30 ccm. of gas were passed from the rectum, the enormous quantity of 103·5 ccm. of hydrogen and carburetted hydrogen was excreted by the lungs. So that we must conclude that from ten to twelve times as much gas passed out by the lungs as by the anus. Tappeiner has suggested—at present not proved—that there are two kinds of organisms concerned, of which one forms carbonic acid and hydrogen, the other carbonic acid and marsh gas, and by the (supposed) greater resistance of the former to acids, he has sought to explain the larger quantity of the former gases in the upper parts of the intestine and of marsh gas in the lower portions. In excessive meteorism, such as is caused by paralysis of the intestines, *e.g.*, in typhus, we find scarcely any carbonic acid and principally nitrogen; an analysis of the gas obtained by puncture in such a case gave me 8·3 per cent. of CO_2, and the remainder nitrogen, mixed with some oxygen derived from the atmosphere, which entered during the experiment. In a woman aged 54, with a stricture of the rectum, which could be kept open only with the help of a bougie, and ordinarily caused fæcal retention and colossal meteorism, I emptied the gas collected in the intestine by means of a stomach tube, and found,

seven hours after food (soup and bread), 6·9 per cent. CO_2, 11·64 per cent. H, 81·03 per cent. N. Ruge found as much as 50 per cent. of marsh gas in human flatus after eating leguminous vegetables.

The more the contents of the intestine pass downwards, the more do they become exhausted and inspissated, and finally are expelled from the bowel in formed or pulpy or even watery masses, the fæces, which may be mixed under pathological conditions with mucus, blood, or pus. For this the rapidity of peristalsis is the decisive factor, the action of which, in the lowest portion of the bowel, is converted from a continuous into a periodic movement. The sphincters close the intestinal canal like a sluice, which only from time to time opens by a sort of regulating action and allows the accumulated matter to pass out. At the same time we must not imagine that such matters only are excreted with the fæces as are no longer useful to the organism. A part of the nutrient matter leaves the body under ordinary circumstances in this way, frequently only slightly changed. This is the surplus of the food which man, "the gluttonous animal," has taken in addition to his needs, and which passes too rapidly through the digestive track to undergo the action of its secretions. The amount of this is naturally dependent upon individual conditions. In the stools of nursing infants, according to Wegscheider, we find coagulated milk, fat, peptones, and even an active diastatic ferment. In adults there are unaltered or only little changed remains of food. In addition there are mucus, epithelium, horny substances, pigments, fatty acids, and products of putrefaction of albumen. Special interest is excited by a substance isolated by Brieger, scatol, a final product of the putrefaction of albumen, which obviously causes the odour of fæces. As abnormal components may be named round (pus) cells, mucus in large quantities, blood corpuscles, and parasites or their eggs.

It is known that defæcation is subject, under normal conditions, to moderate variations in frequency and character. There are people who have two stools daily, others who have one every two or three days, and there have been cases recorded in which the bowels were opened regularly only once in eight or even fourteen days, the general health being quite good. Bristowe gives the maximum at from six to eight weeks. But the actions of

drugs can defer the termination still longer; thus Williams records the case of a lady who, in consequence of the habitual use of opium, had very frequently only one stool in six weeks, and once during a whole year had her bowels opened only four times. The reverse of this is found in the numerous stools of diarrhœa ; indeed in dysentery they may reach thirty or forty in twenty-four hours. Their characters depend upon the secretion of the intestinal mucous membrane, the transudation from the blood, peristalsis and the particular kind of pathological process affecting the intestinal mucous membrane, and last, not least, the special contents of the intestine represented by the ingesta. Sometimes one, sometimes the other of these factors preponderates, and so it happens that the stools undergo great variations, not only in relation to their composition, but to their diagnostic value and pathological significance. Take, for example, the products of an ordinary summer diarrhœa and that occurring in albuminuria or consumption, which, regarded apart from the history, our knowledge does not in any way enable us to distinguish, yet which, in their pathological significance, are very widely distinct. A number of such instances might be given.

It is remarkable how few chemical analyses of diarrhœic stools we possess, if we except cholera and perhaps dysentery. The former is chiefly known from Schmidt's analysis, which I give here, and I place beside it the analysis of a stool produced by infusion of senna :

	Cholera.	Senna.
Water	984·15	969·75
Albumen		1·64
Organic matter	5·15	20·03
Inorganic	8·19	8·58

If we desire to examine diarrhœic stools in practice, it is absolutely necessary not to confine ourselves to simple inspection, but to leave the stool to deposit its sediment in a tall glass. The odour may be reduced to a minimum in both solid and fluid stools, if, as I recommend, a thin layer of ether be poured over it. After settling, we can perceive at a glance the approximate quantities of water and blood, the amount of mucus and solids, the colour of the sediment, and the supernatant fluid; we can recognise far better the quantity and the size of certain fibrinous

exudations which, as you know, are found in so-called diarrhœa tubularis, forming complete casts of the intestinal tube, and, finally, can easily select portions for microscopical examination. The contents—in pus and blood corpuscles, in abraded epithelium, mucus and elements of tumours—permit a conclusion, although only approximatively, as to the intensity and nature of the process going on in the intestine. The method is now greatly extended, especially in all cases where there is choleraic diarrhœa, in which the employment of bacterioscopic methods has become indispensable. If you desire to learn more of these things, which I cannot enter into here, may I recommend you, gentlemen, the magnificent monograph of Nothnagel, "Beiträge zur Physiologie und Pathologie des Darms," as well as the work of Bienenstock, "Ueber die Bacterien der Fäces," and the handbooks of bacteriology.

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LECTURE XI.

Gentlemen,—We have to consider to-day *Absorption*, that is, the processes by which the contents of the intestine pass into the blood and chyle. There was a time, and that not so long ago, when it was believed absorption occurred only by the lacteals. But it is not so. Even the primæ viæ take part in the transference of soluble matter into the vessels, and even in the cavity of the mouth very readily absorbed matter is taken up. But this only is true of very small quantities, differing more or less in nature, but not of the absorption of larger quantities of such substances which it is the object of digestion to serve. This begins in the stomach. According to the experiments of Smith and Anrep, when the stomach was cut off at the pylorus, or separated from the intestine by a plug introduced through a fistulous opening in the duodenum, it was ascertained that sugar and peptone were absorbed in no small amount. In the same experiments it seemed probable that to some extent fat was split up in the stomach, and therefore might be absorbed. However, the greater part of absorbable matter is taken up from the intestine. As we have said, it was at one time believed that this took place only by means of the lacteals, but we know now that the radicles of the portal vein participate in the process. In the blood of the portal vein, between the intestine and the liver, we find sugar, a dextrine-like body, and peptone, which have passed direct from the intestine into the veins, so that we must admit that the blood and chyle vessels share in absorption, although apparently the latter perform the chief part, especially that of taking up fat. In connection with this interesting point, let us first see what is the structure of the apparatus of this absorption, which is the function of the villi. The epithelial covering of the villi presents, according to the most recent researches of Heidenhain, which we shall follow here, three different forms of cell: 1. Absorbing epithelial cells; 2. Goblet cells; and 3. Wandering cells. Chief interest

attaches to the first of these. These present a cylindrical, conical, or pyramidal epithelium, which is so arranged that the broad end of each cell is turned towards the lumen of the intestine, and the apex towards the body of the villus, being separated from the proper parenchyma of the villus by a membranous limiting layer pierced by round or oval fenestræ (Drasch, Watney). According to Heidenhain, they possess no *membrana propria*. During digestion we can see in them numerous oil globules; indeed, Moleschott and Marfels maintain that they have seen in them (in the frog) choroidal pigment and blood corpuscles from other animals which were introduced into the intestine. The remarkable and exceptional character of this epithelium is the so-called "cover" (deckel), which is a small strip closing the cell opposite the lumen of the intestine marked with fine longitudinal striæ, which, when looked at from above, have the appearance of numerous dots. This striation does not extend quite to the lower border, but ends a little higher, so that the "cover" has the appearance of a comb turned with its teeth upwards. This striated or rod-like appearance is presented by the so-called "cover" under all physiological conditions, during fasting as well as during absorption, and, indeed, whether these striæ are pre-formed, or are post-mortem products of splitting of the cell contents—whether they represent a system of fine pores or canals which, to a certain degree, permit entrance to the proper cell cavity, or whether they are only an illusion produced by a kind of cilia possessed by these special cells are points upon which hitherto no agreement has been reached. The last view is defended with great determination by Thanhoffer. According to him, we have to do with moving protoplasmic cell processes, which by their motion draw in the smallest molecular particles, especially fat globules. According to Heidenhain, the cover consists of a homogeneous white mass, into which the rodlets extend, like processes of the protoplasm of the cell. They are not rigid cuticular formations, but plastic processes of the cell body, as, in the event of any very active changes in the form of the epithelial cells, they can be thrust forward to very varying extents. In the middle of the villus, lying between the vein and artery, runs the lacteal, which passes into the submucous tissue, and then takes on the characters of a valved vein. The capillary area of the blood-

vessels is distributed over the periphery of the body of the villus, close beneath the epithelial layer. Between the lacteal and the epithelium lies the proper parenchyma of the villus in the shape of a meshwork of connective tissue, in the spaces of which, besides a few wandering lymphoid cells, lie fixed cells of a different kind. Heidenhain years ago stated that the central lacteal is connected with the epithelium through a system of connective tissue-like cells, whose processes communicate directly with the open apices of the cells. Eimer and Tarschanoff have confirmed this view, which is all the more acceptable as many of the facts of digestion require us to believe in the existence of direct pre-formed channels for carrying the intestinal contents through the epithelium of the villi into the lacteal. There can be no doubt that we find fat which has come from the intestinal contents in the cells of the villi during digestion, and, as is well known, it can be demonstrated with ease in the contents of the lacteals, so that in some way or other it must find its way out of the former into the latter. But the recent careful investigations of Heidenhain, which, unlike the earlier ones, have not been made on the frog but on higher mammals, and with improved methods, lead to the conclusion that the above-described immediate connection between the connective tissue cells and the epithelium of the villus does not exist. The epithelial cells end, for the most part, at the surface of the cell without sending any processes to connect them with deeper lying structures, and the fat moves into the special parenchyma of the villus through pericellular spaces. The same would hold good for soluble food and salts in the intestinal contents as they flow over the villi.

Finally, the villi are provided with a specially-arranged muscular layer, divided into longitudinal and circular fibres. Whilst the former, that is, the longitudinal fibres, have been long known, it was Brücke who drew attention to the existence of the smooth, circular fibres. The arrangement of these muscles has been carefully studied by Mall, Graf Spee, and Heidenhain, who have demonstrated that the longitudinal fibres form a sort of buttress upon which the connective tissue framework in part rests, while arch- or pencil-shaped radiating fibres are given off from the muscles connecting the apices of the cells with their sides. It is clear that by the contraction of this system of longitudinal and transverse fibres (1) the contents of the villus are pumped up

to the tuft of the lacteal, and (2) new material from the intestine is sucked up into the villus, whilst in the intervals of contraction the central canal, by the assistance of the valves already referred to, works in a manner analogous to that of the heart.

As is well known, the intestinal villi are regarded as an "artifice of nature" to multiply the already by no means small surface of the intestinal canal. Heidenhain found that in a square centimetre of dog's intestine there are 2,500 villi; Mall gives a smaller number, namely, 1,600. Taking the first-named number and the measurements of von Spee, and reckoning on the supposition that the average length of a villus is 1·48 mm., the breadth 0·2 mm., the entire absorbing surface of a villus cylinder is 0·969 mm.; therefore a square centimetre of intestinal mucous membrane would, if the villi could be stretched out, cover a surface of not less than 23 square centimetres, so that the absorbing surface is increased more than twenty times.

Let us see in what manner the intestinal contents pass through the villi into the lymph circulation of the intestinal mucous membrane, that is, the absorption of the intestinal contents.

The special process of absorption appears at the first blush as the proposition that the contents of the blood-vessels and lacteals and those of the intestine represent two fluids separated by a membrane, the wall of the villus, behaving as if in a dialyser, an explanation which at first sight offers no great difficulty. It is generally admitted that the exchange between the intestinal contents and the blood follows the laws of diffusion and endosmosis. This may be at once granted in so far as concerns inorganic salts, but not for other substances. The passage of water into the blood would be brought about by the previously mentioned high endosmotic equivalent of the albumen found in the blood, which favours a current of water out of the intestine into the richly albuminous blood; the absorption of peptone takes place in consequence of the great difference in the endosmotic equivalent between it and raw albumen, at least according to physical laws, and the like takes place for solutions of sugar. These views find experimental support in the experiments which have been made, partly by Funke, partly by Becker and others, and which show that solutions of common salt, sugar, and peptone, injected into ligatured loops of intestine, disappear from the loop in more or less time in proportion to their concentration. But it

is plain that such experiments can teach us only the fact of absorption and the practical conditions respecting it, not the details of the processes themselves. It has been shown that the presumed higher diffusive capacity of peptone is actually very slight (Adamkiewicz, Maly), and cannot at all explain the phenomena of absorption. Nevertheless it is true, and has been proved by comparative experiments, that peptone leaves the intestine and passes into the circulation more rapidly than unchanged albumen, and that with it and the salts large quantities of water are taken up from the intestine. Heidenhain injected water coloured with methyl-blue into a ligatured loop of intestine, then killed the animal, and examined the wall of the bowel microscopically. By this means he convinced himself that the absorbed water passed through as well as between the cells. In further experiments he measured the quantity of water present in the contents of a loop of intestine, and also the quantity of chyle absorbed therefrom in a given time; the difference between these two factors gave the quantity of water taken up by the blood-vessels, and showed that they take up by far the greatest quantity of the water absorbed. This accords with an earlier observation of Zawilsky, namely, that the quantity of lymph is not much greater during digestion than while fasting. But all these are, I might say, only secondary facts, and the forces which effect the transfer of water and albumen, or albumoses and peptones, into the lacteals and blood-vessels are by no means explained, whether one describes them as "vital processes," or labels them as a series of unknown chemical and physical processes. We stand in face of just such an unexplained fact as we encountered in connection with the absorption of fat, though one may say that, contrary to earlier views, the absorption of fat has become more intelligible to us, while the absorption of albumen presents more difficulties than ever. Fat does not diffuse at all, or at least not in a manner extensive enough for the purposes of absorption. Nevertheless we find after a fatty meal free fat in the chyle and blood, and it may be seen in its resting-place in the epithelium of the villi, on its way from the intestine to the blood. There are here many possibilities. Either the fat in substance enters the lacteal through the membrane of the villus, for which there must be some provision to make the process mechanically

possible; or the fat is decomposed chemically and split up into diffusible and absorbable components, which then at some place —not to be accurately defined—unite again to form fat; or, finally, the fat is taken up by some easily moving elements (wandering cells), and transported by them through the parenchyma of the villus into the lacteal, where it is again set free. For all these possibilities there is some kind of evidence, but the question cannot be decided in one direction or the other. Respecting the mechanical absorption of fat, we may at present speak as follows: a fundamental condition for the absorption of fat in substance is obviously its division so finely that single droplets can pass through the epithelium or the pores of its covers. For this purpose the fat must be emulsified, that is, the fat must be divided, either by mechanical or physical force, in the presence of a more or less viscid menstruum, into small spherules, which, according to the goodness of the emulsion, remain apart for a longer or shorter time, then coalesce to form large drops, and finally to become a compact layer of fluid fat. But such fine emulsions, as was formerly believed, are to be obtained outside the organism only by the employment of strong mechanical forces, which cannot by any means be attained by the musculature of the intestine, and we were always in a dilemma how to explain the formation of the emulsion obviously present. You see now the significance of Gad's proof of the self-emulsification of fat, which we have already spoken of in detail, especially as this investigator has made it probable that the fine fat-drops of the emulsion described do not surpass the diameter of an epithelial pore. The emulsification of fat in the intestine takes place partly in this way, partly through the pancreatic juice and the animal gums contained in the intestinal mucus. The latter —the animal gums—possess, according to Landwehr, great fat-emulsifying properties, and are separated from the intestinal mucus through the action of the bile. We may place alongside this statement, which has not yet been confirmed, the self-emulsification of fats, as Gad describes it, which is easily demonstrated at any time by a certain and easily performed experiment; and the very important question as to the force by which fat is subdivided in the intestine finds a satisfactory answer, in the smallest and least apparent forces, which here, as so often in Nature, produce mighty results, if its effect or at least its rôle as one

of the factors in the absorption of fat had not been established by a number of independent observations. It is easy to demonstrate that after eating fat the intestinal villi are covered with a cream-like layer, which consists of microscopic fat droplets, but these fat spherules are not far removed in their minuteness from the powder-like division of fat met with in chyle. There is, however, wanting the soap or free alkali ordinarily necessary for the formation of such an emulsion. Schmidt-Mulheim, J. Munk, and Cash have found the reaction of the intestinal contents of a dog after feeding with fat to be acid throughout; while Munk and Cash found no emulsion, only fat in large drops, in the intestinal contents of an animal fed with fat; and, finally, v. Frey showed that the chyle-formed emulsion differs from other emulsions, in so far that the latter disappear on acidulation, but the former is stable, while, on the other hand, for the formation of an emulsion by shaking, as that of the chyle is formed, no soap is necessary. The acid reaction of the intestine is not, for many reasons, so important as at first sight it appears to be. I may remind you of the experiments of v. Lindenberg, already described, which established the remarkable fact of the activity of trypsin in lactic and acetic acid menstrua, and I may ask whether a good emulsion may not be formed by pancreatic juice even in acid intestinal contents, when this reaction is caused by small quantities of free lactic acid or acid salts. In the second place, my case of duodenal fistula shows that the intestinal contents after fatty food have at least a neutral and not an acid reaction, and I would suggest the question whether the acid reaction may not be a consequence of the splitting up of a certain amount of fat, and whether free fat is still found merely because there is too much to be dealt with all at once. Finally, Cl. Bernard has shown that pancreatic emulsions differ from other emulsions by occurring in acid solutions. So that the possibility of the formation of emulsions on a large scale for the purpose of absorption is by no means excluded, and is much better founded than the opinion that fluid fat is absorbed without any previous emulsification. The experiment of von Wistinghausen affords a basis for the latter view, according to which bile or its acids exercises an influence over the rising of oil in capillary tubes, and, consequently, in the

capillary pores of animal membranes. The experiment is as follows:—

Two almost capillary glass tubes, of which one is washed inside with a solution of bile acid, and the other with a solution of soda or with water, are dipped side by side into a glass of oil. The oil rises in both by capillary attraction for some distance, but reaches about a millimetre higher in the tube containing bile acid than in the other.

Further, bile acid favours the passage of fat through damp animal membranes; and as the epithelium of the villi in the intestine is bathed in bile, this circumstance, in connection with the facts discovered by Wistinghausen, greatly elucidates, if it does not solve, the question of the passage of fat through the pores of the epithelium into the commencement of the lacteal. Still, Gröper has recently made some observations which call in question Wistinghausen's experiments. He studied the relations of various fluids to the absorption of fats in capillary spaces, and proved in the capillaries of blotting paper, wool fibres deprived of their grease, and animal membranes, that soaking these substances with bile or water made no difference to their permeability for oil. But such assistance would only be needed if the fat globules were too large to pass through the pores without resistance; otherwise they would be suspended in the stream of fluid which runs from the intestine to the lacteal, and they would be subject to the same laws of motion as this. Meanwhile the striation of the basal border, formerly taken to be due to pores in the epithelium, is, according to more recent statements, much more probably caused by ciliated processes, a pre-formed canal system being therefore absent. Finally, J. Munk and F. Müller have shown in almost corresponding researches that even fat, the melting temperature of which is above the body temperature, for example, spermaceti, which first melts at 53° C., is absorbed freely. Here purely physical processes such as are concerned in Wistinghausen's experiment cannot be in question. Nevertheless it is certain that the bile, as we have already seen, plays an important part in the absorption of fat, only, unfortunately, we must place after the how? a very large note of interrogation.

Zawarykin and Schäfer have lately made statements which at first sight appear very fascinating. It is known with what

eagerness the lymph-corpuscles take up foreign bodies and transport them by means of amæboid movements from place to place. Such elements on the surface of the epithelium of a villus become charged with fat droplets, or almost corpuscular fat, which they carry through the epithelium into the lymph spaces of the villus, where they may be met with in all stages of their progress, and by treatment with osmic acid black fat droplets may be demonstrated in them. Here we have the ants which labour at the carriage of non-emulsified or undecomposed fat, and furnish us with a happy solution of a much-laboured controversy, which even the obvious objection, that the cells always carry fat and never other corpuscular elements (pigments, &c.), cannot damage. We may explain this by supposing that they possess a certain selective power. But the facts do not support the hypothesis. Wiemer has undertaken a careful inquiry into this question, and concludes that though a small amount of fat may be found enclosed in lymph-corpuscles between the epithelial cells and between these and the central lymph space, the greater part is free, and must have found its way in a free state into the epithelium. This view is substantially that taken by Eysoldt as the result of studies published from the Physiological Institute of Kiel on the absorption of fat; and Heidenhain says in his most recent and much-quoted work, after having given many reasons and adduced the circumstance that black granules in cells after treatment by osmic acid do not necessarily prove the presence of fat, that "it is scarcely possible to think that the leucocytes play an important part in the transport of fat." It is not to be doubted, according to this investigator, that fat, even in large drops, is found within the epithelium, and that it moves within the pericellular spaces of the parenchyma of the villi, whence the greater part of it passes into the central lacteal, whilst any absorption by the capillaries of the villus, if it does take place at all, is at most doubtful.

But are we then thrown back upon the passage of fat in substance in order to explain the milk-white appearance of the chyle after fatty food? By no means. Indeed we have learnt many other factors which show us that the mechanical absorption of fat, if it occurs at all, is only small in amount. Cl. Bernard sought for an explanation of this absorption in the property of

pancreatic juice discovered by him, by which it splits neutral fats into glycerine and the corresponding fatty acids. It is true that this was found only in an executed criminal. As is well known the blood contains soluble soaps, that is, combinations of fatty acids with soda or potash, and it appears very plausible to admit that these are formed in the intestine by the alkalies introduced with the food out of the decomposed fat, and absorbed according to the laws of diffusion. Thus it is very well explained how soaps are formed in the intestine and gain entrance to the blood, but not how fat as such gets from the intestine into the vessels. Younger investigators have, therefore, gone a step further, and have sought to prove that both the components of fat, the glycerine and the fatty acids, make their way separately from the cavity of the intestine into the villi, and are first reconverted by synthesis to form fat, either in the epithelial cells themselves, or at least on their way to the thoracic duct, in which by some a previous saponification of the fatty acids is accepted. This standpoint is taken by Will and Perewoznikoff, who hold that the regeneration takes place in the epithelium of the villi. Will fed animals with palmitic acid and glycerine, as well as with pure soap made from palmitic acid and glycerine, and found in both cases a marked fatty infiltration of the intestinal epithelium, in which after treatment with osmic acid the fat droplets were stained deep black, a test against which, however, we have seen Heidenhain protests. J. Munk proved by exact experiments, quite recently confirmed by Walther in Ludwig's laboratory, that the balance of tissue metamorphosis in a dog remains the same, whether he is fed with fat or a corresponding amount of fatty acids; but he found that fatty acids, like fluid fats, are emulsified in feeble alkaline media, and considered that, given a certain richness of fatty food, the available alkali is not sufficient to saponify the resulting fatty acids, and that these are taken up in the form of an emulsion. On the way to the thoracic duct this emulsion must in great part be reconverted into fat, as the chyle of such animals is milk-white (as in feeding with fat), and chemical analysis shows that it contains besides the fatty acids a considerable, and indeed absolutely large amount of neutral fat. He found about 38 times as much as in the thoracic duct of a starving dog, and 20 times as much as in the thoracic duct of a dog fed on meat, whence he was able to conclude that not only

fatty acids belonging to such fat as is normally present in the bodies of dogs, but also quite different kinds of fat, such as pigs' fat or mutton suet, could be in this way utilised in large quantities in the animal body. Synthesis of the absorbed fatty acids so as to form neutral fats, and their utilisation in the organism, is not to be doubted, but it is very doubtful if we can look upon this as the only or even the chief condition of fat, as P. Walther in repeating and continuing the experiments of Munk found that when fatty acids were introduced into the intestine a part of them were converted even in the cavity of the small intestine into glycerides, that is, neutral fats, the very opposite condition to that which is desired, according to Munk's views, for the absorption of fat. So that we are not much nearer a final settlement of this question, as none of these experiments make the particular process of fat absorption intelligible. We must accept a compromise between the chemical and mechanical theories. There is a chemical decomposition of fat, then a mechanical carriage of the resulting emulsion of fatty acids, and finally a chemical regeneration (synthesis) of this emulsion with the postulated glycerine to form fat. No recent attempt has been made to solve this puzzle!

As to the place where the necessary synthesis occurs, we may venture—as they appear to be confirmed by results—to give the conclusions of my experiments, according to which the so-called surviving intestinal mucous membrane, that is, the mucous membrane of a recently killed dog carefully separated from the muscular and serous coats, possesses the power of forming fat from soap and glycerine. Unfortunately I have not been able of late years to continue these experiments and to make the proof complete.

From all this, gentlemen, you see that we have only an uncertain and shifting basis for our knowledge of this important process, and that there is much yet to be done upon it. But are the physical laws as at present known sufficient to explain the transference of the entire intestinal contents from the cavity of the intestine to the vessels, even if we admit that the whole of the matter to be transferred is physically transferable, *i.e.*, diffusible? This cannot by any means be affirmed without reserve. Voit and Bauer have drawn attention to many facts which do not agree with simple diffusion or endosmosis. Only we should not need

to fall back upon endosmosis and diffusion if we accept, with Brücke, a periodical contraction of the musculature of the villi, as before mentioned, a sort of pump action in the villi, which, *mutatis mutandis*, works like the heart; or if we accept the view that the mechanical force of peristalsis drives the contents of the intestine into the blood and chyle vessels by a sort of filtration under pressure. But a pump ought to work regularly, and, without distinguishing between fluids of different composition, it should make the contents of the well (the intestine) come through the pipe (the cells and first lymph spaces) into the trough (the lacteal). But in the present case it is not so. We know that different substances in solution in the intestine do not pass into the chyle, and we have had this demonstrated by Tappeiner's experiments upon the variations in the absorption of bile acids in different portions of the intestine. The observations of Lannois and Lépine also prove that the entire upper portion of the small intestine absorbs better than the lower, but under certain conditions—obviously when the epithelium is irritated—this becomes equalised. Moreover, leucin and tyrosin have never been found in the repeatedly examined portal blood or chyle, although these bodies are formed by the pancreatic digestion, and the former at least is quite soluble in water. Simple pumping certainly does not take place, but the stimulated muscular action serves only as a means of motion for the stream once set in motion in the lacteals; and we may remember that the valves of the lacteals, beginning in the submucous coat, must promote this by preventing reflux. But this theory does not explain the passage through the epithelium. The following suggestions of Hoppe-Seyler find their place here: 1, fat can pass undissolved into the chyle through the intestinal epithelium independently of the villi (in the lower animals); and 2, the absorption of water from the intestine into the blood is dependent upon healthy living epithelial cells, and simple irritation of these cells suffices to turn the stream from the blood and lymph into the intestine. Finally, Hoppe-Seyler adds, that a series of toxic substances, phosphorus, arsenic, preparations of antimony and jalap, abolish or diminish absorption by killing or irritating the cylindrical epithelium. The first and last of these points seem to me to be most important. The transudation of water into the intestine originates not in the irritation of the epithelium, but in

the vaso-motor nerves. We can completely kill the epithelium of a mucous membrane with nitrate of silver without causing a trace of œdema, which, however, occurs at once when substances which act more deeply are employed, and quite the same takes place on the external skin. In the second case also, the normal absorption from the intestine would be surpassed by the transudation out of the vessels, and therefore no conclusion would be possible from this condition as to a special function of the epithelium. But the above points are less easily rejected by the adherents of the physical theory of absorption.

Ludwig has drawn attention, through his pupil Zawilsky, to the fact that the quantity of fat present in the chyle is independent of the amount of water; whilst the view of a general filtration through the epithelium (whether endosmotic or mechanical by means of the muscles of the villi) would make a direct relation between fat and water very probable. If we were to ascribe the absorption to the laws of diffusion alone, when a dilute-solution of alcohol is injected into the intestine, water should pass out of the blood into the intestine, while just the reverse occurs. Thus Brieger found by experiments which he performed according to the method of Moreau (p. 165), that 0·5—1 per cent. solutions of neutral salts were followed by no transudation into the ligatured intestinal loops, but 20 per cent. solutions produced a clear yellow alkaline fluid, containing shreds of mucus, epithelium, and mucous granules, so that irritation of the mucous membrane was a necessary stimulus to the process, which we were always accustomed to regard as simply due to the high endosmotic equivalent of the neutral salts. The objections thus multiply against the view that absorption is a purely physical phenomenon, and Hoppe-Seyler's description, although provisionally only an hypothesis, must receive the greatest consideration, "that absorption takes place mainly through chemical affinities, conditioned by the life of the cell, which is thereby itself changed and used up."

Gentlemen, the foregoing words were written by me five years ago, and I have only to add to them, that though the views stated have made way scarcely one investigator has devoted himself to the exclusively physical theory of absorption. Apparently they compound the forces of absorption out of three factors, chemical, physical, and mechanical. Though Heidenhain

has calculated that the movement of fluid in intestinal absorption is very slow, so that for example it takes five minutes to pass through the epithelial layer—Lehmann found on injecting iodide of potassium into a loop of intestine that the first traces were found in the blood of the mesenteric vein five minutes after—yet the force which impels the fluid along the lacteals must be a powerful one. If the thoracic duct is tied (Schmidt-Mulheim), or occluded by new growths, the mesenteric lymphatics are filled to bursting, and there is expansion of the perivascular spaces in the neighbourhood of the mesenteric lymphatic glands, the pancreas, &c.

Where does absorption take place, and what is absorbed? The first is as easy as the second is difficult to answer. That the entire intestinal tract, from the stomach to the sphincter ani, participates in absorption in different degrees in different parts, has been placed beyond doubt by numerous observations and investigations. We have already spoken of the absorption of sugar from the stomach, and have only, parenthetically, to add that the absorbing capacity of the gastric mucous membrane for substances which pass easily into the blood, as, for example, iodide of potassium, has recently been used for diagnostic purposes. Penzoldt found the period of absorption to vary in health between 6½ and 15 minutes (proved by giving iodide of potassium in gelatine paper capsules, and testing the saliva at short intervals with starch paper), whilst in chronic gastric catarrh and dilatation this is greatly increased, so that the reaction does not occur for half an hour or more (Wolff, Faber, Quetsch, Zweifel, Häberlin). But even on fat the gastric mucous membrane is not entirely without influence. At least Ogata found, in Ludwig's laboratory, that neutral fats were decomposed in the stomach to fatty acids, and Cash observed, during the digestion of freshly minced gastric mucous membrane, fat and a little hydrochloric acid, a direct formation of fatty acids. Klemperer and Scheurlen performed experiments on men by introducing pure oleic acid or chemically pure olein into the stomach, and after an interval withdrawing the stomach contents for investigation. They found that though 1—2 per cent. of the neutral fat was decomposed in the stomach—partly by the action of certain bacteria, but chiefly attributable to a physiological action of the gastric mucous membrane—yet no absorption of neutral fat or

free fatty acids occurs in the stomach. However, this does not agree with certain experiments which I have made by introducing a mixture of oil and starch paste into the stomach. I found after a certain variable but never constant lapse of time, that the proportions between the quantities of oil and starch paste present had undergone a change, which would not be the case were it simply a question of their passage into the duodenum. So that I am obliged, in order to explain this recurrence, to admit that there is a certain absorption of fat by the wall of the stomach.

On the other hand there can be no doubt of the absorption of peptone from the stomach, which appears to keep pace with its production, as Schmidt-Mulheim has found that the proportions between peptone and albumen in the expressed contents of the stomach remain the same throughout all stages of digestion. We are also justified in regarding the stomach as the place in which the process of absorption of nutriment into the vessels first begins, as we must also maintain that it reaches its maximum in the small intestine and diminishes again lower down. Even the large intestine, however, possesses, according to Voit and Bauer, a certain capacity for absorbing fat (of 12 grms. of goose fat injected, 2·2 grms. disappeared). Special interest attaches from a practical point of view to the question of absorption from the large intestine, which, thanks to Leube, plays in recent times a beneficent part in therapeutics by the use of nutrient enemata based thereupon. Leube has shown, as you know, that compounds of minced meat, fat, pancreas, and water, injected per anum into an animal in a state of nitrogenous equilibrium, can maintain it in this condition for some time without any food being given it by the mouth, and he has applied this in practice with the happiest results. This combination is intended to peptonise the meat by means of the pancreas. Its preparation is a little particular, as the product often irritates the bowel, especially after long use, and is quickly expelled. We have now available much better preparations in the various manufactured preparations of peptone-albumose—Leube's solution, Kemmerich's meat peptone, Adamkiewicz or Sanders-Ezn's peptone, Antweiler's albumoses. It is certainly impossible that a healthy person, much less a sick person, can be nourished for any length of time by the rectum, although each part of the intestinal tract can act

vicariously at times for others, because all the principal factors are, so to speak, in duplicate; yet the co-operation of all the factors is needed for the scantiest nutrition: without it no extensive absorption is possible. Voit and Bauer in their best case could only effect the absorption from the rectum of about a fourth part of the albumen necessary to life, with the addition of fat or hydrocarbons. The great value of nutritive enemata is not so much in prolonging the lives of patients with incurable strictures, carcinoma, &c., which make feeding impossible by the mouth, as by permitting complete rest in acute affections of the upper part of the digestive tract; and in this sense their employment is, to my mind, still much too little generalised amongst the profession. Finally, I must not omit that Savory maintains that there is a more rapid absorption of drugs from the intestine than from the stomach. The action of those administered by the mouth is weakened, partly from changes which the substances undergo from the gastric juice, partly from their dilution in the chyme.

The next question, *what* is absorbed? points chiefly to the bodies arising from normal digestion, as we have learnt to recognise them, and the products of the complicating processes. Thus peptone, sugar, probably dextrine-like bodies, salts, water, gelatine, glycocoll, fat, and soaps, perhaps also leucin, are directly taken up, as is proved by the presence of these substances in the blood and tissues. So, too, with some of the bodies ascribed to the putrefaction of albumen, indol and phenol, which we find again, although in an altered form, in the urine as indican and phenyl-sulphuric acid. On the other hand, we know no positive facts which permit the view that undigested albumen on the one hand, or the remains of putrefactive products on the other, as well as a series of organic acids—acetic, butyric, capronic, valerianic acids—partly introduced with the food, partly formed by fermentation of the hydrocarbons, do pass into the blood, or let us know the magnitude of this passage if it actually occurs. We are just as little informed as to how far the gases, carbonic acid, hydrogen, marsh gas, sulphuretted hydrogen, and ammonia, which are developed in these processes, find their way into the blood. But by what channels do the absorbed materials travel? Are they exclusively the lymph (chyle) vessels, or do the radicles of the portal vein participate, and to what extent?

These questions, old as the discovery of the lymphatic system by Avelli, Rudbeck, and Pacquet, were first decided by Magendie in the sense that absorption takes place in both ways. An animal dies after the introduction of a soluble poison into its intestine, although the thoracic duct is tied. A glance at the white distended lacteals of an animal during the digestion of fat, proves that fat exclusively or mainly goes this way. Respecting sugar, v. Mering has proved that it passes into the blood, and no demonstrable amount can be found in the chyle. The same fact is known respecting many salts; for example, sulphindigotate of soda, while others, such as sodium chloride, are distinguished by the fact that they are not taken up in proportion to their concentration, but that the relation between water and salt absorbed differs, as Gumilewski has shown, according to the concentration of the solution, so that in weak solutions (0·25 per cent. NaCl) more water is absorbed than salt to correspond, while in stronger solutions (from 1 per cent.) more salt than water. Moreover, we know that albumen and blood are constituents of the portal blood as of the chyle. But very remarkably we find after the richest albuminous meal only traces of peptone in the blood; indeed, Neumann found that even when great quantities of peptone were present in the intestine, only the slightest traces were to be found in the blood or the lymph; and, even when peptone is injected into the blood, it can only be demonstrated in traces for a few minutes. Nevertheless, the blood has always much albumen, about 8 per cent., and if peptone is digested with blood, outside the organism, it remains unchanged, wherefore it follows that the blood contains no substances which can destroy peptone. The peptones must, when taken up, be very rapidly reconverted into albumen, or it may be that albumen as such is absorbed.

The question whether unchanged albumen coagulable by heat passes into the blood and becomes used up in nutrition, is sometimes affirmed, sometimes denied. Bernard and Pavy have proved that dissolved albumen, casein and globulin, injected into the blood, reappear in the urine, and pass unchanged through the organism. It is known that after heavy meals a slight amount of albumen is occasionally present in the urine, a circumstance which appears to speak in favour of the passage

of unchanged albumen into the blood. In fact, possibly a small part of undigested albumen may pass directly into the blood; but by far the greatest quantity of the albumen which forms our tissues and circulates in our blood, originates undoubtedly from peptone changed back again into albumen, which is effected, as shown already, by simple anhydration, a process which we find so often in the organism. The possibility of this is fully proved by the experiments of Maly, Plosz, Adamkiewicz, and others, which agree in showing that feeding with pure peptone is sufficient for animal nutrition. We cannot see anything in the entire process of peptonisation, or in the transformation of sugar into starch, but a chemical contrivance which the organism employs in order to transport large masses of material in the shortest possible time and in the purest possible form. When this is effected, the animal body has at its command another means, anhydration, or the removal of water, to again consolidate the matter in question into its original form or one of its allied forms, and to store it up for use. Whether this occurs, as Hofmeister believes, through the agency of the colourless cells of the adenoid tissue, or in some other fashion, must remain for the present an open question. Heidenhain holds, in opposition to Hofmeister's view, that the quantity of absorbable (dried) albuminates, which can pass into the circulation within twenty-four hours, is much greater than the total weight of the fresh mucous membrane, which contains, besides blood corpuscles, glands, blood-vessels, epithelium, and connective tissue, and that, according to his calculation, 80 grms. of fresh lymph corpuscles, possessing only 20 grms. of dry material amongst them, must assimilate 274 grms. of dried albumen, which would require an enormous power of subdivision on the part of the leucocyte, which microscopic examination of them does not suggest. Brücke, the most determined representative of the view that unchanged albumen is absorbed, has found ordinary unchanged albumen in the lacteals, and moreover shows that a completely dissolved digestive mixture of pepsin, albumen, and hydrochloric acid, after neutralisation and removal of the precipitated syntonin, gives, on heating, a precipitate of coagulable albumen; and he argues, that if such solutions are absorbed, the coagulable albumen contained in them must be absorbed too. The first observation, made by such a careful

observer, is, unless we have to do with some anomalous condition, of great weight. But the presence of coagulable albumen in apparently digested digestive mixtures, on which Brücke lays great stress, is due, as I have repeatedly proved, simply to incomplete digestion. If the digestion in such a solution be started anew by the addition of some fresh pepsin and hydrochloric acid, after a short time there is no longer any albumen present coagulable by heat. So much appears to be certain, by analogy with many other processes, that all digestive actions proceed more quickly inside the organism, and their products occur earlier, than we can imitate with our retorts and incubators. But, on the other side, the experiments of Eichhorst and myself have shown that unchanged albumen injected into the rectum is absorbed, and can maintain the nitrogenous equilibrium, although no peptonising function is possessed by the lower portions of the bowel; and the quite unexpected and paradoxical discoveries of v. Ott, Nadina Popoff, and J. Brinck, have shown that peptone or albumen solutions introduced into the stomach or intestine give rise to the formation of serum-albumen in the cavity of the organ. The obvious objection that they had to do with an exudation of blood serum from the wall of the cavity and not with a reconversion of peptone into serum-albumen, is not discussed in the works in question, but appears to be excluded, as this peculiarity occurred only with stomach peptone but not with pancreas peptone.

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LECTURE XII.

Gentlemen,—The intestinal tract forms, from the beginning to the end, a continuous canal into which the various gland ducts open like tributaries, their specific secretions being not isolated, but mingled complexly in it. There obviously exist also certain reflex connections between the various organs. Richet, in his patient with gastric fistula and stricture of the œsophagus, saw that when food was introduced by a tube into the stomach the salivary secretion was increased, and on chewing sapid and odorous substances a proportionally strong flow of gastric juice occurred. Moreover, according to the investigations of Hüfner, Munk, and Kühne, the various secreting organs possess not only the main specific properties described in the previous chapters, such as the action of ptyalin in the saliva, and that of pepsin in the gastric juice, but it may be easily proved that the actions of one gland approach in some degree to those of the others. Thus J. Munk found that saliva treated with hydrochloric acid digested fibrin and formed peptone; and, on the other hand, that a diastatic ferment could be separated by glycerine from the stomach and intestinal mucous membrane. Kühne records the same, but he also proves that trypsin is found only in the pancreas or its secretion. The experiments of Ogata, according to which the stomach splits up neutral fats into glycerine and fatty acids, have been related in the previous lecture. These are, however, accidental or at most concomitant phenomena of each special gland function, and indeed we can obtain similar slight ferment actions, not only with the glands *κατ' ἐξοχήν*, but with many other tissues, such as the lungs and the blood.

Does one secretion prevent the action of another? The saliva is swallowed in great quantity, and must, as often stated, be rendered inactive by the acid gastric juice; and, conversely, by its alkalinity it may neutralise or alkalinise the reaction of the gastric juice, so as to stop the pepsin digestion. The latter is possible, but must be very rare, being possible only in the presence

of excessive sialorrhœa, and is more imagined in theory than observed in practice. At least I know of no such cases either in literature or my own practice, and we could (Ewald and Boas) mix good active human gastric juice with an equal quantity of saliva, without noticeably affecting its digestive power. Sticker has observed that saliva excites the secretion of gastric juice, as in a female patient suffering from dryness of the mouth due to diminished secretion of saliva, with painful dyspepsia, he found the hydrochloric acid of the gastric contents, which was at first diminished, became later on excessive when by appropriate means he was able to stimulate the salivary glands to secrete abundantly.

The influence on the diastatic ferments of the mixture with acid has been recently investigated in quite a large number of researches —we should name in the first rank the careful and thorough investigations of Professor Chittenden of Pennsylvania—and the general result is that very small quantities of hydrochloric acid, between 0·0005 and 0·001 per cent. increase the amylolytic action of the saliva a little, but that larger quantities diminish or destroy it. Physiological gastric digestion has to do with the formation of great quantities of reducing substances where the food is rich in starch, and this apparently only fails to occur under pathological conditions when there is an excessive formation of acid (hypersecretio acida). Still we could show (Ewald and Boas) that the quantity of products of starch conversion does not remain the same during a period of digestion, but after a preliminary rise diminishes in proportion to the increase of acidity which during the same time rises from a low figure to its maximum. In general, also, the highest amount of reducing substances corresponds to the smallest amount of acid and *vice versâ*. For example, five minutes after drinking a boiled 2 per cent. starch solution, the degree of acidity was 0·05 per cent., and the reduction equalled 0·282 of sugar, and fifteen minutes later, with 0·275 of acid, 0·052 of sugar were found. These figures depend not only on the formation of different mixtures, but, as we have already shown, on the absorption of the products. So that it may be that the reduction figure may remain the same during a long time, even for the whole of an experiment lasting forty-five minutes, whilst the acidity is increasing. At all events the reducing substance is formed in the first minutes or seconds, and

the later acidity can only affect the fermentation by controlling it. We must therefore, in order to study the controlling effect of acids on the action of the saliva, proceed as in a laboratory experiment, that is, add the acid to the starch and then drink it. In such experiments it appears that an acidity of hydrochloric acid of 0·07 to 0·1 per cent., or of lactic acid of 0·1 per cent., checks the formation of reducing substances. On the other hand, bile, when it occurs in the stomach under pathological conditions, as we proved by experiment, stops the gastric digestion by forming, according to Burkart, a precipitate which mechanically throws down the pepsin. But at the same time you saw that a relatively large quantity was required to effect this, whilst smaller quantities had no influence on the gastric digestion, so that under ordinary conditions, in which only a small reflux of bile occurs, there can be no interference with the gastric digestion. We (Ewald and Boas) have found in our healthy subjects of experiment the gastric contents or its filtrate quite bright green, and have demonstrated the presence of bile pigment by Gmelin's test, but we are not able to decide how far this may have been due to the irritation caused by the introduction of the stomach tube.

In the duodenum the pepsin digestion proceeds so long as the reaction is still acid; but as soon as it meets the bile, the syntonin and peptones are precipitated, the swollen albuminoids shrink up, and the pepsin is carried down mechanically with the precipitate. Then, with the assistance of large quantities of bile and pancreatic juice, the precipitated albumen becomes redissolved, and the digestive process recommences. But this description has the fault of being too theoretical, as if things inside the intestine passed through the various phases and distinct stages that we see and learn from our artificial digestion experiments. When we remember that the distance from the pylorus to the opening of the d. choledochus is uncommonly short (about 8 cm.), and that there the bile duct and pancreatic duct open immediately together, and that whilst by the action of the bile the foregoing reactions are proceeding, the pancreatic juice is at the same time present to reverse them, the process cannot be split up into distinct phases, but the actions of the bile and pancreatic juice must be understood to be bound up together most intimately. If we allow alcohol and sulphuric

acid to act upon each other, ether is formed; but between the two, ethyl-sulphuric acid occurs, which we do not notice, because it is immediately transformed. Similarly there are no externally noticeable effects of the bile, because its products at once undergo further chemical changes, that is, are subjected to the pancreatic action. Boas has contrived, in accordance with our above described observation, a simple method of obtaining the contents of the human duodenum by the use of massage to press back the duodenal contents into the empty stomach, from which they are withdrawn by means of a stomach tube. We have already explained that by this method we can derive no new ideas as to the physiological action of the contents of the small intestine, or obtain its mixed secretions. We only get a mixture of the latter *plus* chyme, and can with it, as Boas has shown, demonstrate the known action of intestinal digestion. On the other hand, it affords a splendid means of studying the opposed action of the gastric juice, or chyme, and the secretion of the intestine. In the first place, it shows that, contrary to the general opinion, the contents of the intestine so obtained are feebly alkaline or neutral, containing abundant bile pigment, yet do not throw down pepsin on the addition of acid or acid gastric juice, or only to a very small extent. If we mix bile containing intestinal contents with an equal amount of gastric juice, so that an abundant thick precipitate takes place, and after leaving it to stand for twenty-four hours, draw off the upper layer of the mixture with a pipette, and add to it so much stomach filtrate that it contains free hydrochloric acid, it is found to act on albumen. Further, it is found that the addition of hydrochloric acid, in the same degree of concentration as it is met with in the stomach, to bile, which, as is known, putrefies easily, very quickly acts as an antiseptic. Such an acid mixture has no tryptic or saccharifying action. If we dissolve the precipitate by addition of iodine solution we obtain the proteolytic and diastatic action of the pancreatic juice, though this is only possible in the first two or three hours after the mixture is made; later on no active intestinal contents can be obtained by alkalinisation, and Boas confirmed the statements of Kühne and myself, that trypsin is destroyed by peptic digestion, although coming to quite an opposite conclusion. It is true that, according to Boas, "the gastric contents freed of ferment by

heat" are equally able to destroy the ferments of the pancreatic juice, and this injurious action must be ascribed only to the effect of the hydrochloric acid.

In the subsequent divisions of the intestine, the bile and pancreatic juice co-operate in the digestion of fat, as we have related above. Finally, in how far putrefaction in the lower part of the intestine affects the normal pancreatic digestion, and whether both processes run synchronously, or precede or follow one another, is uncertain. Langley, who has undertaken a methodical investigation of the relations of the digestive ferments to one another, concludes "that the special ferments of the various portions of the digestive tube are each respectively destroyed in the succeeding portion." However, the enzymes, according to F. Falk, appear to possess a great power of resisting the action of putrefaction. But we do not eat albumen, starch, that is hydrocarbon, and fat, or the different organic and inorganic acids and salts, in a pure condition, but take these things in our food in the most complicated and variously compounded shapes. Let us follow some of the most ordinary food on its way through the digestive tract, and see how far, how quickly, and when it is absorbed. This will be scarcely more than a retrospect over the path we have been treading, and the employment of the knowledge we have gained about articles of food, points which, strictly speaking, are included under dietetics. Still we shall not examine the various foods in their composition, digestibility, metabolic importance, and so on, but review various groups in respect to the relations of their nutrient parts to digestion. Once again, as before, I would ask your attention to the dependence of the digestibility of food in a very high degree—a healthy condition of the digestive tract being presumed—upon its penetrability by the digestive fluids. Fats, which we so willingly abuse as indigestible, are decidedly not so. They are easily absorbed, and even a certain degree of rancidity is, as we have seen, rather favourable than otherwise. Naturally they must not be eaten in excess, as in that case all, even the best Swiss milk, is indigestible, that is, it causes mechanical changes, or cannot be absorbed before the whole becomes decomposed, and gives rise to the necessary consequences. The great rôle which the goodness of the food, its preparation, its composition, the rapidity of eating, and many other things, play in digestion, I

dare not enter upon farther. These things belong to dietetics or metabolism. In this place we can only deal with the general principles which are determined in the digestion of the great groups, and we may submit some considerations as to their employment in particular cases. It will be better to take the different groups *seriatim*, and for simplicity we will regard milk apart from "drinks."

1. *Drinks.*—These consist of watery or alcoholic solutions of salts, organic matter, acids, and gases, and are probably completely and rapidly absorbed in the stomach. However, we must not assume that this process is very rapid. I have followed it by introducing a stomach tube as far as the pylorus and connecting the other end to a graduated vertical burette, so that between the mouth of the person experimented on and the lower end of the burette the tube formed a U. When the stomach and the tubes were filled with water, the burette placed at about the height of the cardia, and care taken that the person remained quiet, a communication was established between the stomach and the fluid in the burette, so that the position of the water in the burette represented the level of the water in the stomach. This level naturally oscillated under the influence of the thoracic and abdominal pressure, but the level sank continually lower, though slowly, so that at the end of an hour and a half, for the experiment was not continued longer, it had fallen only 10 to 20 cm. We shall say more respecting this and experiments with other drinks in another place. In dilatation of the stomach fluids may remain there an abnormally long time, and then perhaps they undergo decomposition. Thence arises the feeling of fluctuation which we so frequently find on palpating dilated stomachs, and the beneficent results of washing out the stomach in such cases.

2. *Ordinary albumen.*—This in the dissolved condition is probably for the most part converted into peptone in the stomach. If coagulated, it requires a longer time, until the edges of the masticated fragments are dissolved by the operation of the gastric juice. Uffelmann saw the contours of such pieces unchanged after two hours, and the aspect externally under the microscope was that of a finely granular mass. Blondlot found that a dog with a gastric fistula digested 100 grms. of albumen whipped to froth in $3\frac{1}{2}$ hours, and 100 grms. of cooked albumen in 5 hours. We

ordinarily regard eggs as pure albumen, and forget the not unimportant yolk contents of fat and salts, the former of which does not become absorbed in the stomach. Yolk of egg is nothing more than an emulsion of fat in solution of albumen, which, according to Prout, contains 17 per cent. of albumen, 29 per cent. fat, and 54 per cent. water. The eggs of the cayman of the Orinoco are used, as Sachs relates, for making oil.

3. *Albumen and fat as milk.*—The coagulation of milk in acid gastric juice begins almost immediately after its introduction. It is at first slight, and increases in the first half-hour to its maximum. Casein and fat are gradually separated in more or less compact flocculi or lumps, which are at first sparingly suspended in a milky fluid, but after a short time become more numerous and larger. Therewith the complete separation takes place into curds (fat and casein) and whey (salts, lactose, and water). The latter is absorbed in the stomach. The coagulum consists of closely aggregated fat globules imbedded in an amorphous mass, together with other constituents of the stomach, such as casein, starch granules, and muscular fibres, surrounded by coagula which frequently are covered by mucus. Mother's milk differs from cow's milk not only in its chemical composition but, as Biedert has shown, in the way it curdles, namely, in small flakes, instead of in large lumps. As the work of the digestive juices is facilitated by being able to penetrate more easily and rapidly the material they have to dissolve, we regard this curdling in small flakes as an advantage in mother's milk over cow's milk, and it has been attempted, not without success, to confer upon the latter this property by artificial means. Casein-peptone is formed from these clots partly in the stomach, partly in the intestine, and absorption of this and of the fat takes place. The so-called milk-detritus, which is so often found in the shape of yellowish white flocculi in the stools of healthy infants, consists, according to Wegscheider, far more of fat, and indeed of olein, palmatin, stearin, and a little peptone, than of unchanged albumen. On the other hand, it is certain that, under pathological conditions of the digestive tract, much unchanged casein, syntonin, and other albuminoids are excreted. Closer investigations are still needed respecting these very important conditions.

4. *Albumen in the form of meat.*—It is to be noticed that the

muscular fibrillæ are surrounded by the fibrous perimysium, and the muscular bundles by tendon and fascia. The gastric juice cannot get at the albumen-containing fibrillæ until these coverings are removed, ruptured, or dissolved. This happens as they are converted into gelatine, and is dependent upon the resistance of the fibres. These are harder in old flesh than in young, and stronger in raw than in cooked meat. By maceration in hot water the connective tissue is softened and removed. The *post-mortem* action of acids acts in a similar manner, and we promote this by hanging meat. The muscle-glycogen is changed into lactose, and the connective tissue is loosened by the resulting acid. Raw meat is on this account less easily digestible than cooked meat. But what we lose on one side we gain on the other, as the albumen of the fibrillæ is not coagulated, and so is easily peptonised. By cutting up the meat we endeavour to make the connective tissue as small as possible; and in fact many ill-nourished children and dyspeptic adults digest raw meat better than cooked. In this respect the so-called steamed meat and underdone roast meat preserve the proper medium. We have discussed already the further transformations of the primitive muscular bundles under the head of gastric digestion. The soluble constituents of meat, such as creatin, creatinin, extractives, salts, &c., are, so far as they are soluble in acid solutions, absorbed in the stomach; the principal part passes as chyme with the loosened and softened, but not destroyed, fragments into the small intestine, and is then absorbed or transferred to the large intestine, and eventually excreted. The same happens to the fats which are eaten, partly with meat, partly with the accompanying matter.

5. *Fat and fatty acids.*—These are not absorbed in the stomach and commencement of the duodenum on account of the excessively acid reaction. In whatever form they are ingested, whether alone, whether in combination with other nutriment, or contained in the latter, they are always separated from the other constituents and remain intact until acted upon by the bile and pancreatic juice. We have already discussed the details of the process of absorption. But we may add that, according to Ludwig's investigations (Zawilsky), the passage of fat into the lacteals after a copious meal increases up to the fifth hour after taking food, and remains at the same height to the twentieth

hour, then sinks to the thirtieth hour, and about this time ceases with the disappearance of the ingested fat from the intestinal canal. Animal fats are more easily emulsified than vegetable fats, and Gad has proved, in his experiments already described to you, that castor-oil, under the conditions of his experiments, generally forms no emulsion. A not insignificant quantity of fat passes into the fæces, partly as free fatty acids, partly as soap, but a part at present still escapes our observation. Zawilsky found, by simultaneous examination of the gastro-intestinal contents, the chyle and the blood, after ingestion of fat, that more fat always disappeared from the intestine than could be found in the chyle and blood. The quantity of fat in the chyle in 22 hours=84·1 grms., while during this time 132·0 grms. disappeared from the intestine, and other experiments make it extremely probable that this deficit passed somehow directly into the blood. It disappears again tolerably quickly from the blood, as thirty hours after a copious ingestion of fat the blood has regained its normal amount of fat. What becomes of the glycerin derived from the fat, whether it is directly taken up as such, for which the fact of the increase of the liver glycogen after ingestion of glycerin says something, or whether it is decomposed, is unknown.

6. *Vegetables.*—Fruits and pot-herbs: we obtain principally from these our necessary hydrocarbons, and, to a less extent, albuminates. Only the most wretched pauperism or the eccentricity of the vegetarian allows a vegetable diet to suffice; yet as we do not live, like savages, on meat alone, the civilisation of the world is bound up with the knowledge of agriculture. But the assimilation of the protein substances contained in them, of the hydrocarbons, organic acids, and salts, is opposed by the difficulty that most vegetables are covered by an envelope of cellulose not easily penetrated by the digestive juices, and carry a ballast of woody cells, epidermis, chlorophyll and other pigments, which in part only undergo absorption. The more, by preparation, boiling, baking, preserving, and the like, we make the cell contents, the digestible matter, capable of being affected by the digestive juices, the more easily can the hydrocarbons, the sugar and gum, form absorbable solutions, and the proteids, principally casein from altered legumin, be transformed into peptones. Therefore raw pot-herbs, such as salads, are almost entirely unassimilable, and

are excreted nearly unchanged. The digestibility of cooked pot-herbs, fruits, and leguminous vegetables is in proportion as, in cooking, the cellulose is loosened, softened, and the cell contents made accessible. Vegetables possess a nitrogenous constituent, legumin, which is a body resembling casein in all important properties, and gluten, which is very like syntonin, into which plant fibrin and plant gelatine become transformed. This albuminoid becomes in part directly dissolved, in part changed into peptone and so absorbed. Among hydrocarbons we must mention the different kinds of starch and sugar, namely, amylum, dextrin, achroödextrin, inulin, sorbite, &c.; pectin material, gums and vegetable mucus, especially present in pith, fleshy fruits and roots, which are changed into grape sugar, partly in the stomach, partly in the small intestine, but part of which, namely, the pectin and mucus, remain unchanged; whilst the relations of a third group, to which inulin, gums, inosite, and sorbite belong, are not yet made certain. I have already described how these hydrocarbons undergo further decomposition by fermentation, and what products are formed from them. Finally, we must add the almost overlooked series of organic compounds, which, in part directly with vegetables, in part as mediate derivatives of them, serve partly as nutriment, partly as gratification of taste, partly as medicine. They, as well as the inorganic salts, come under observation only so far as they are soluble, or are decomposed into soluble compounds, or can form such. Their absorption occurs chiefly in the upper part of the intestinal tract, and they are of no further interest to us in the study of digestion. Now how far the food is changed and absorbed, and what part not used by the organism is expelled with the fæces, belong to the study of nutrition, which cannot be pursued further here. Only to give an example of the amount of loss by the simplest food in its passage from the mouth to the anus, we may state that Rubner found in a meal of peas a loss of 17·5 per cent. nitrogen, 63·9 fat, 3·6 carbo-hydrates, and 32·5 ash, which were not absorbed, but were excreted in the fæces. Naturally such figures must vary greatly according to the individual and the kind of ingesta.

There arises another trivial, but still important question in practice. How often and at what times should we take food?

Between the extremes of the carnivora, which feed once in

twenty-four hours or even longer, and the herbivora, which never have done with the business of feeding, man holds a middle place, but not without permitting the recognition in the course of his life of a sort of transition from the herbivore to the carnivore. Infants should have the breast as often as they wake during the first three weeks; after that, every two hours to the third month; then every three hours up to the dentition; and later there should be five meals in the twenty-four hours. The last is also true for adults, provided that the principal and secondary meals alternate regularly. Still the intervals between different meals are often too long, between others too short. It is so partially with us, but is especially the case in England and America, where the custom is to eat a large breakfast and then go till evening without eating hardly anything, and at six o'clock to take another meal, naturally then in abnormal quantity. This not only causes inactivity of body and mind, which always accompanies the digestion of large meals, but is the cause of numerous disorders of the digestive system, especially the stomach. Chronic gastritis, dyspepsia, atony of the mucous membrane, and dilatation of the stomach, result from the excessive irritation of the organ. But while the disproportional filling of the stomach after a long pause is injurious and irrational, on the other hand our digestive organs are quite capable of receiving moderate quantities of food and digesting them within a given time. Feeding, if very prolonged, or only interrupted by short intervals, as in herbivores and infants, would be an unnecessary waste of labour and time. Under certain pathological conditions and in the convalescence of severe diseases, every patient should in this sense be again an infant or a herbivore. The more often and the less at one time he takes of food, the easier will the enfeebled digestive organs be accommodated. Here the time spent by the physician and the patient in discussing the kind and choice of food will not be lost.

The time of day for meals follows the distinctions of country, town and city, so that no stringent rules can be laid down. It depends too much upon custom and social conditions. The greatest economy of the day would indisputably be attained if the principal meal were taken in the afternoon somewhere between five and seven, so that there should be four instead of five meals daily. This is physiologically permissible provided

there is a light but nutritious midday meal, the luncheon of the English. Then naturally our so-called "abendbrod" (supper) loses its substantial character and is limited to something to eat and drink. For there is nothing more irrational than to take a large meal late at night and just before going to bed. I may remind you of the results of Busch's investigations, which show a complete cessation of the digestive function during the night; and this is sufficiently confirmed by the broken sleep, restlessness, nightmares, dreams, bad taste in the mouth, &c., which result from late and heavy meals. Yet these simplest and commonest physiological rules are constantly being transgressed, and an intelligent system of dietetics offers a fruitful field for successful work. The relations between the functions of the brain and stomach are well known, and "inability to sleep at night" originates frequently in a fasting stomach. It is a repeatedly proved experience that sleeplessness after long evening work is cured by taking a little bread, cake, or the like, just before going to bed.

So much for these matters, which properly fall within the range of dietetics.

Gentlemen, I have now reached my appointed limits. We have traced the digestive process through its various stages, and the action of the apparatus which effects this process has been analysed so far as possible in its different phases, in its structure and its various constituents. We may hope that a not distant future will widen the sure field of our knowledge by new and lucid investigations, while we do not seek to conceal that this progressive development, here as elsewhere, will be dangerous to many established, still intact, or already tottering theories.

As we have seen in the course of our discussion, processes go on in our organism which do not harmonise with the limited application of the combustion theory to the processes of retrogressive metamorphosis, and we gain new support day by day for the view that our body not only, as was formerly supposed, breaks up the ingested nutriment and makes use of the products of decomposition as such, but that it builds up out of these new compounds, and performs not only destructive but synthetic processes; so we see in the limited field of the subject of Digestion a decided revolution against the theories of the

schools. The hard and fast lines within which the processes of digestion were included, for the sake of, one might almost say, a certain utilitarian principle, attractive as they are by a kind of popular comprehensiveness, can be maintained no longer in their full extent.

Quite apart from the fact that we now can discern better the functions of the participating glands, especially the pancreas, according to the kind and energy of their action, we were too much inclined earlier to regard the various digestive factors apart from each other, and to make artificial limits which practically do not exist, just as we—especially in considering absorption—used to ascribe too large a field to the action of physiological forces, and too small a field to chemical forces. We have seen how the fermentative actions of various digestive juices resemble each other, how the physiological glandular actions and putrefactive processes are allied to one another, how physical and chemical forces are not separated but work in common, and how, as a new factor, the specific forces of the living cell, which we provisionally must admit, although still inexplicable, come into play; in short, how processes take place, in truth, by the co-operation of numerous factors, which sometimes aid and sometimes hinder them, and which are more complicated than we can reproduce with our retorts, dialysers, and air-baths, outside the organism; and still the latter is the unavoidable and correct way to trace the more delicate processes of digestion. Such investigations are of great and primary significance. But we must not forget that under all circumstances we need the control of experiments on the living organism whenever we can provide the necessary experimental conditions, or a pathological process gives us the necessary material.

In this matter all of us may assist, and by a single good pathological observation, such as the latest publication of this kind, Demant's researches on the intestinal juice, or my own case of præternatural anus, and the recent investigations of J. Munk, on a patient with a lymphatic fistula, give important aid to scientific medicine. But this requires a knowledge of the present position of the questions *sub judice*, so that you may follow easily the evolution of such a rapidly growing and advancing department of knowledge as the subject of Digestion now is.

But we owe physiology still more than we can repay. I need not insist again upon the importance of the knowledge of physiological phenomena for the right understanding and treatment of pathological processes. In immediate connection with the experiments of physiologists, in part directly stimulated by them, practitioners have in late years successfully turned these views to account in pathology. Many most excellent clinicists have recently directed their energies to this department of knowledge. The use of the stomach-pump, nutritive enemata, artificial nutriment, and digestive preparations, gives eloquent testimony to this. When I concluded these "Lectures on Digestion" twelve years ago, I felt warranted in ending with the following words: "But there is still much to be done, and a large field lies open to our common labour. The best result of our meetings would be if they should awaken in you, gentlemen, a new and lively interest in this important branch of our knowledge." To-day this wish has been brilliantly fulfilled. Numerous workers, physiologists and pathologists, have in the last few years taken up the subject of digestion with extraordinary zeal, so that, apart from bacteriology and its triumphs, there is scarcely another branch of our knowledge in which such interest has been taken. How much has been gained, not only of fast-flying chaff, but of sure bases for our knowledge, you may see by comparing the first with this, the third edition of these lectures. May the future bring equal interest in and an equal measure of work on digestion in its physiological and pathological relations, then the physician will no longer have to complain, as he has to do to-day, in spite of all the work accomplished, of the inadequacy of the diagnosis and treatment of disorders of digestion.

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